

**New Organometallic Strategies for Conjugate
Addition and Cross-Coupling Reactions**

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Abstract

Enamine *N*-oxides have been reported only a very few times in the literature. Investigation into their reactivity has revealed that treatment with catecholborane can generate amines *via* an electrophilic iminium species, which provides evidence for a proposed reverse polarity reactivity, with respect to existing 1,4-additions to nitro alkenes. Deprotonation at the α -carbon of enamine *N*-oxide double bonds has also been accomplished by ^tBuLi, with deprotonation occurring fully after 5 min. Using methodology developed within the group, a novel enamine *N*-oxide has been synthesised in good yield, although attempts to form a cyclic enamine *N*-oxide were unsuccessful.

The copper-catalysed asymmetric conjugate addition of trimethylaluminium to nitroalkenes was found to give moderate enantioselectivity (46 % ee) using Cu(OAc)₂ and a phosphoramidite ligand in diethyl ether. Conjugate addition of dimethyl(alkynyl)aluminium reagents to cyclic and acyclic enones has been achieved in a racemic sense in good to excellent yields employing MTBE as the solvent with three equivalents of alkynylaluminium, although regioselectivity remains an issue depending on the enone substrate.

Cross-coupling of dimethyl(alkynyl)aluminiums with aryl bromides, iodides and triflates catalysed by Pd₂(dba)₃·CHCl₃ or Pd(dba)₂ and DavePhos gave acetylene derivatives in good to excellent yields. These results are comparable with previously reported systems and in some cases gave improvements in yield. Using XPhos as ligand and adding DABCO, chlorobenzene was also coupled in moderate yield. Application to tetracene synthesis was not successful.

Development of a novel method of alkyne hydroalumination using dichloroalane bis(tetrahydrofuran) adduct and catalytic Ti or Zr metallocene complexes gave high yields of vinylaluminium reagents. Use of these reagents in Pd-catalysed cross-coupling with aryl halides gave good to excellent yields of (*E*)-alkenes, and is applicable to both aryl and alkyl terminal acetylenes.

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Abbreviations

%wt	percentage weight
1,2-DME	1,2-dimethoxyethane
9-BBN	9-borabicyclo[3.3.1]nonane
acac	acetylacetonyl
Aib	2-aminoisobutyric acid
BDE	bond dissociation energy
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
CAN	cerium ammonium nitrate
CatBH	catecholborane
Cp	cyclopentadienyl
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
DABAL-Me ₃	bis(trimethylaluminium)-1,4-diazabicyclo[2.2.2]octane
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DIBAL-H	diisobutylaluminium hydride
DPEN	diphenylethylenediamine
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
E	electrophile
ee	enantiomeric excess
EI	electron impact
<i>ent</i>	enantiomer
er	enantiomeric ratio
ESI	electrospray ionisation
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoric triamide
HMQC	heteronuclear multiple quantum coherence
IMes	1,3-dimesitylimidazol-2-ylidene
Leu	leucine

LDA	lithium diisopropylamide
<i>m</i> CBA	<i>meta</i> -chlorobenzoic acid
<i>m</i> CPBA	<i>meta</i> -chloroperbenzoic acid
Ms	mesyl, methanesulfonyl
MTBE	methyl <i>tert</i> -butyl ether
N.D.	not determined
Nf	nonaflyl, nonafluorobutane sulfonyl
NHC	<i>N</i> -heterocyclic carbene
Nu	nucleophile
PE	petroleum ether
pin	pinacolato
PMB	<i>para</i> -methoxybenzyl
Pro	proline
TADDOL	2,2-dimethyl- $\alpha,\alpha,\alpha^1,\alpha^1$ -tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF	tetra- <i>n</i> -butylammonium fluoride
TC	thiophene-2-carboxylate
Tf	triflyl, trifluoromethanesulfonyl
TM	transition metal
TMS	trimethylsilyl
Trp	tryptophan
Ts	tosyl, toluenesulfonyl
wrt	with respect to

CHAPTER 1

Enamine *N*-oxide Synthesis and Reactivity

1.1 Introduction

The chemistry of enamine *N*-oxides **1** (**Figure 1**) has been virtually unexplored, with only a handful of examples of these compounds being described in the literature. However, recent work within the Woodward group developed a simple method to access enamine *N*-oxides, dramatically increasing the number of compounds known.¹

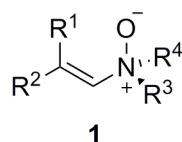


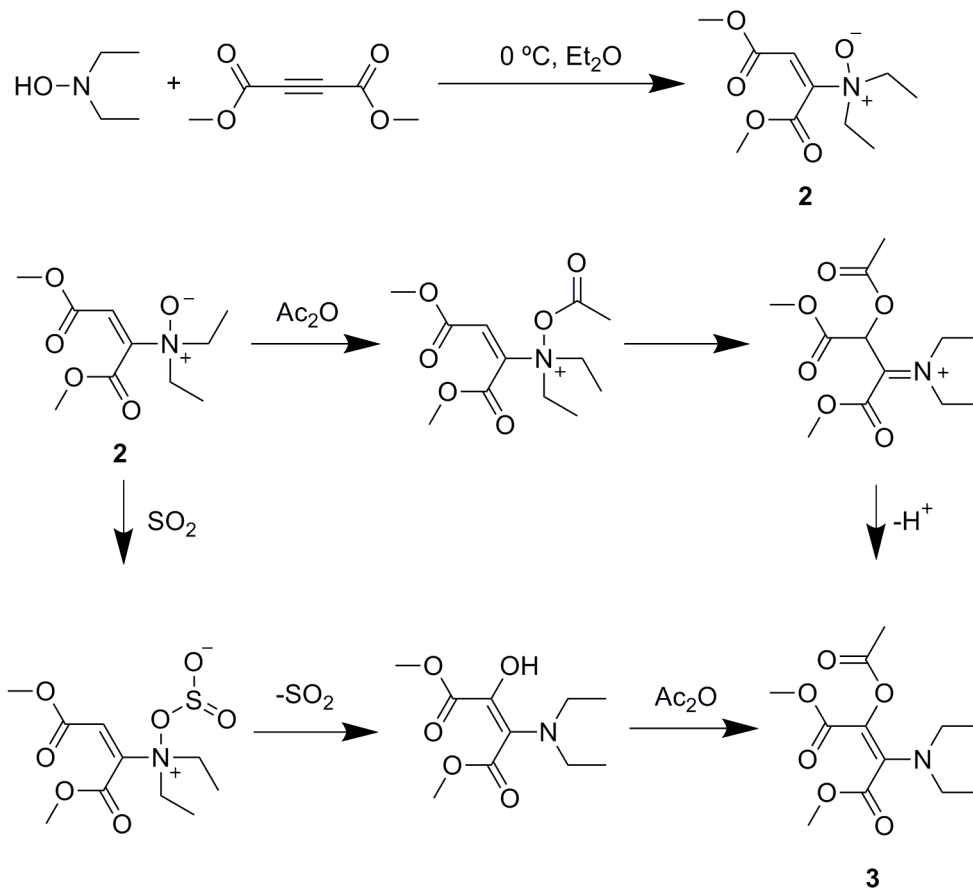
Figure 1

The first example of an enamine *N*-oxide was published by Winterfeldt and Krohn in 1969.² Reaction of *N,N*-diethylhydroxylamine with dimethyl but-2-ynedioate at 0 °C in diethyl ether yielded enamine *N*-oxide **2** (84 %). On treatment with acetic anhydride, or with sulfur dioxide and then acetic anhydride, the enamine *N*-oxide gave enol acetate **3**, *via* an iminium or enol species respectively (**Scheme 1**). In contrast, reaction between *N*-hydroxypiperidine and dimethyl but-2-ynedioate occurred at the *O*-terminus of the hydroxylamine.

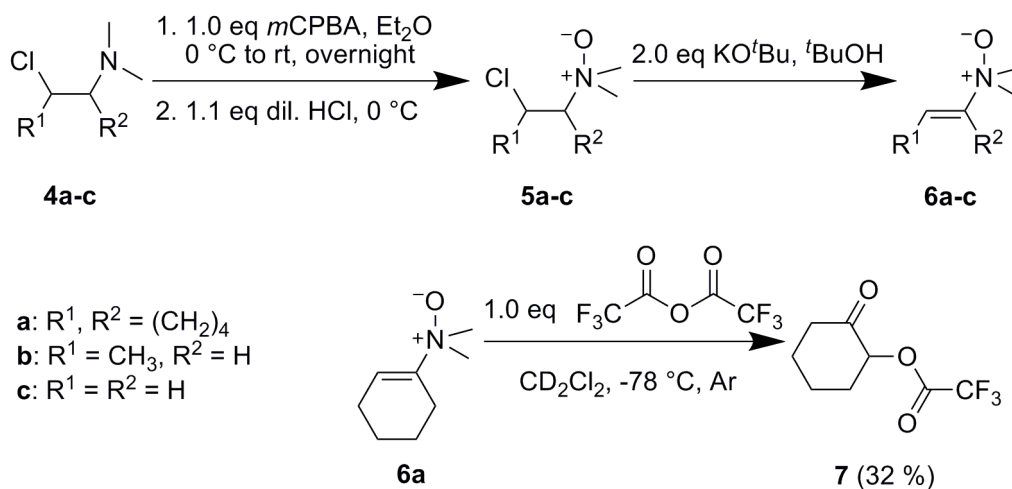
Krouwer and Richmond reported three further enamine *N*-oxides in 1978.³ These were prepared by *m*CPBA oxidation of the corresponding β -chloroamines **4a-c** to their *N*-oxides **5a-c**, then elimination with KO^{*t*}Bu in ^{*t*}BuOH to give enamine *N*-oxides **6a-c**. The reactivity of **6a** was also studied, with a range of acylating agents (e.g. trifluoroacetic anhydride) giving variable yields of 2-substituted cyclohexanones **7** (14-78 %). Titanium tetrachloride was found to yield 2-chlorocyclohexanone in modest yield (47 %), and ^{*n*}BuLi had only limited success in deprotonating **6a** (**Scheme 2**).

Hwu and co-workers briefly described the generation of an enamine *N*-oxide intermediate in an intramolecular cyclisation *en route* to the pyrrole moiety of indoles.⁴ It was postulated that species **8** underwent proton transfer to give

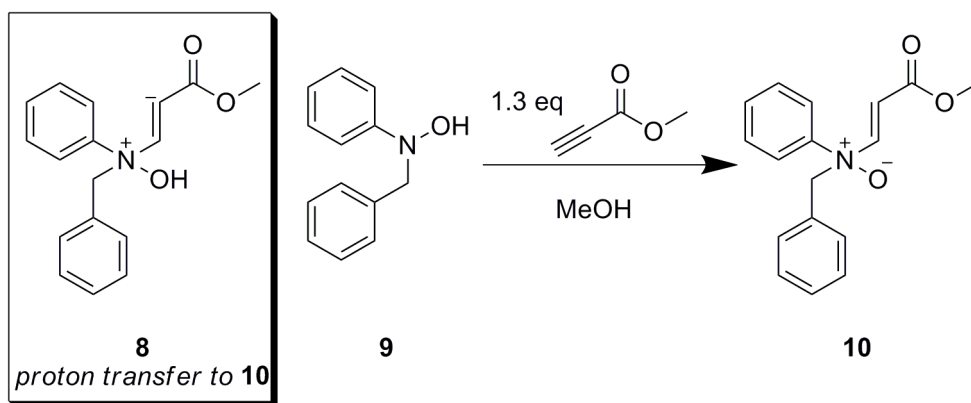
enamine *N*-oxide **10**, and reaction of the synthetic starting materials, hydroxylamine **9** and methyl propiolate, in methanol, did indeed lead to the enamine *N*-oxide **10** (Scheme 3).



Scheme 1

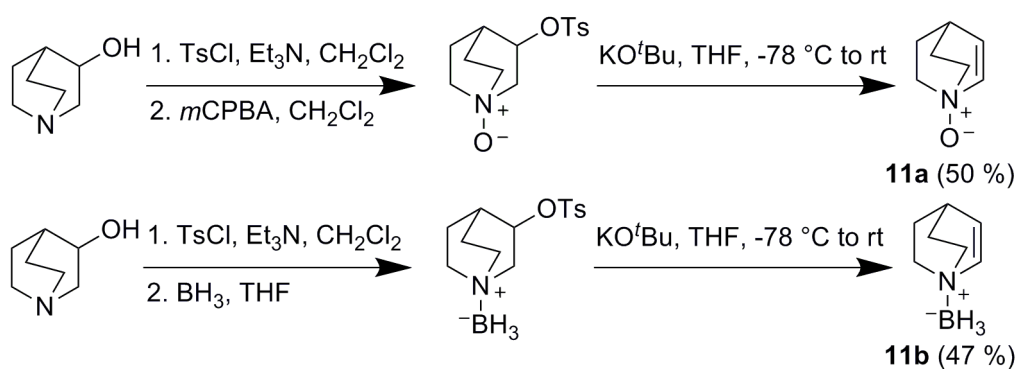


Scheme 2

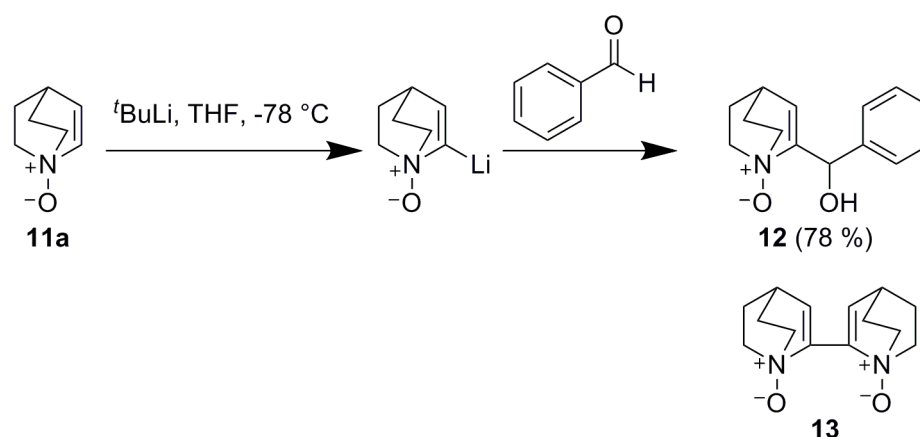


Scheme 3

In a development of their use of quinuclidine *N*-oxide to replace carcinogenic hexamethylphosphoric triamide (HMPA), the O'Neil group synthesised quinuclidine enamine *N*-oxide **11a** (**Scheme 4**).⁵ This was achieved with good overall yields in a similar fashion to the above synthesis of Krouwer and Richmond, with the analogous enamine *N*-borane **11b** also being synthesised by replacing *m*CPBA oxidation of the amine with reaction with borane in THF. In an effort to generate an *N*-oxide species with increased metal-binding properties, namely dimer **13**, enamine *N*-oxide **11a** was deprotonated with one equivalent of ^{*t*}BuLi and trapped with a variety of electrophiles in mostly high yields, for example hydroxybenzyl-substituted enamine *N*-oxide **12** (78 %), as shown in **Scheme 5**.



Scheme 4

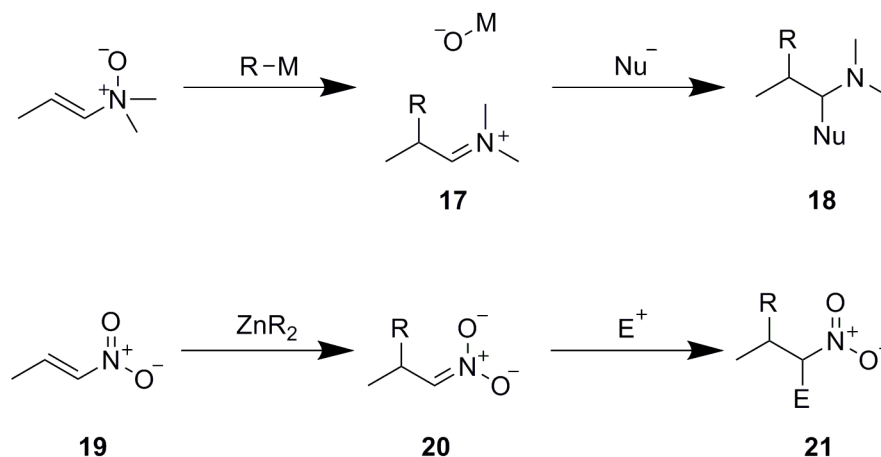


Scheme 5

Work in the Woodward group has modified the syntheses of Krouwer and Richmond, and O'Neil, to allow a variety of enamine *N*-oxides to be synthesised in high yields from commercially available alkenes, β -chloroamine hydrochlorides, or secondary amines (**Scheme 6**). The conditions developed minimise the competing Owari rearrangement of the chloroamine *N*-oxide **14** to an *O,N,N*-substituted hydroxylamine **16** (**Scheme 7**). This rearrangement occurs if the negatively charged oxygen attacks the carbon bearing the chloride to generate an oxazetidinium species **15**. Subsequent attack by either chloride or *m*-chlorobenzoate (from the *m*CPBA used in oxidation to the *N*-oxide), opens the azetidinium at the carbon bearing the positively charged nitrogen to give the rearranged product.

$$\text{R}-\text{C}(=\text{O})$$
$$\text{H} \quad \text{O}^-$$

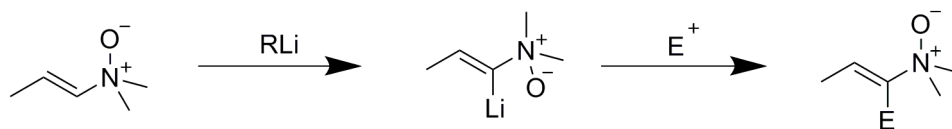

provide an Umpolung alternative to existing methodology, where conjugated nitroalkenes **19** can be treated with an organozinc nucleophile to give a nucleophilic nitronate intermediate **20** in a Michael addition-type manner.⁷ These intermediates can then react with an electrophile to give 1,2-disubstituted nitro compounds **21**. At present there is no reverse polarity equivalent of this approach.



Scheme 9

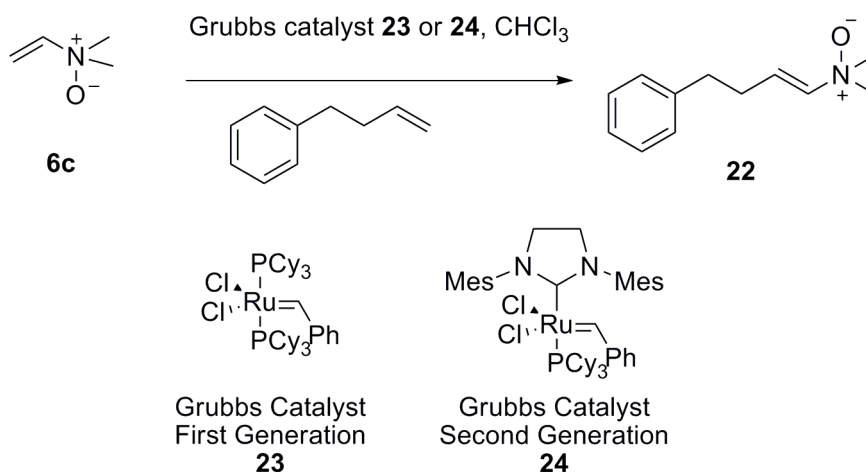
In order to study this reactivity, it was first necessary to synthesise several enamine *N*-oxides using the Woodward group's existing methodology. Having done this, it was intended to treat the enamine *N*-oxides with a range of nucleophiles in an attempt to achieve the desired Umpolung addition. If this was successful, the next objective would be to develop a catalytic, asymmetric protocol which would allow the synthesis of enantiopure compounds featuring contiguous chiral centres not previously accessible. This could be potentially useful for pharmaceutical and natural product synthesis.

In addition to Michael-type chemistry, treatment of enamine *N*-oxides with alkyllithium bases was another area of interest. Deprotonation at the α -carbon of the enamine and subsequent trapping with an electrophile would allow for a variety of substituents to be added to the double bond, whilst leaving the enamine *N*-oxide intact (**Scheme 10**). This approach could be used to influence reactivity, and create heavily functionalised molecules.



Scheme 10

Another goal of the project was to develop shorter, simpler routes to enamine *N*-oxides. Indeed, in Winterfeldt and Krohn's original synthesis, the enamine *N*-oxide was obtained from a hydroxylamine and an alkyne in a single step. The ester di-substituted alkyne used was activated towards attack by the hydroxylamine by the electron-withdrawing esters, and in order for a one-step process to be generally applicable to a variety of substrates, a different method of activation would be necessary. A potential alternative would be to use gold catalysis, which has precedence for activation of alkenes and alkynes in the literature.⁸ Other areas of investigation were the direct reaction of a hydroxylamine with other electron-deficient alkynes, and synthesis *via* a cross metathesis approach where a simple, small enamine *N*-oxide **6c** could be reacted with a variety of alkenes to afford, for example, enamine *N*-oxide product **22** (**Scheme 11**).



Scheme 11

Other work within the group has exploited the Owari rearrangement as a synthetically useful transformation.⁹ Conditions can be used to favour the rearrangement over enamine *N*-oxide formation, and external nucleophiles such as cyanide, azide or thiol, rather than *m*-chlorobenzoate or chloride, can

attack the oxazetidinium intermediate. Further development of this methodology, potentially leading to azides for use in click chemistry was also targeted.

1.3 Results and Discussion

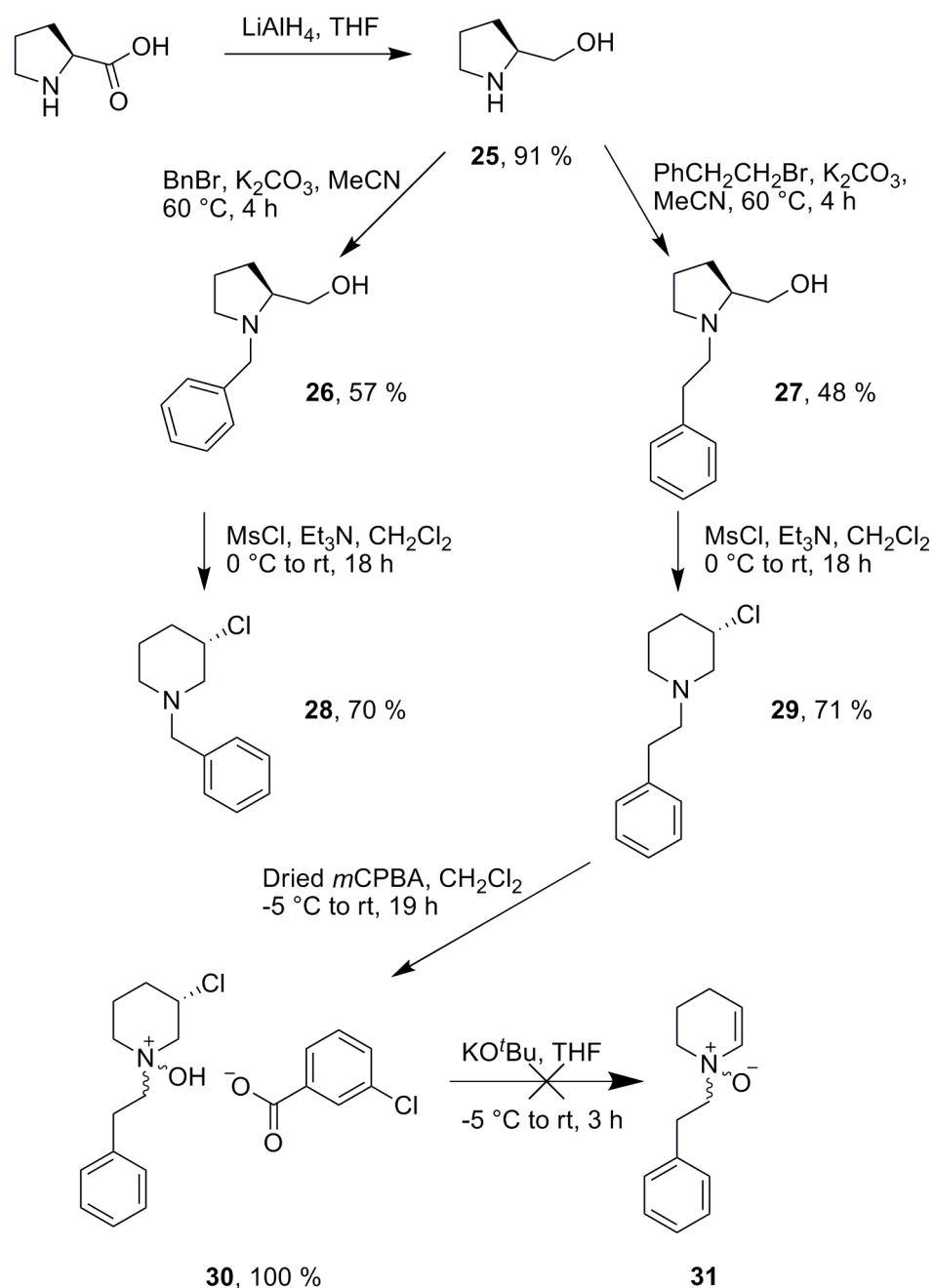
1.3.1 Attempted Synthesis of a Cyclic Enamine *N*-Oxide

Following the precedent for stereoselective oxidation of six-membered cyclic amines using *m*CPBA reported by O'Neil, the application of this approach to synthesis of a cyclic enamine *N*-oxide.¹⁰ It was envisaged that the oxidation of a cyclic β -chloroamine followed by elimination of HCl would furnish a novel cyclic enamine *N*-oxide. The synthesis of the requisite β -chloroamines **28** and **29** was planned to occur by chlorination and ring expansion of the corresponding 5-membered ring aminoalcohols **26** and **27** on treatment with mesyl chloride. The aminoalcohols would be obtained by reduction of *L*-proline and subsequent *N*-protection (**Scheme 12**).

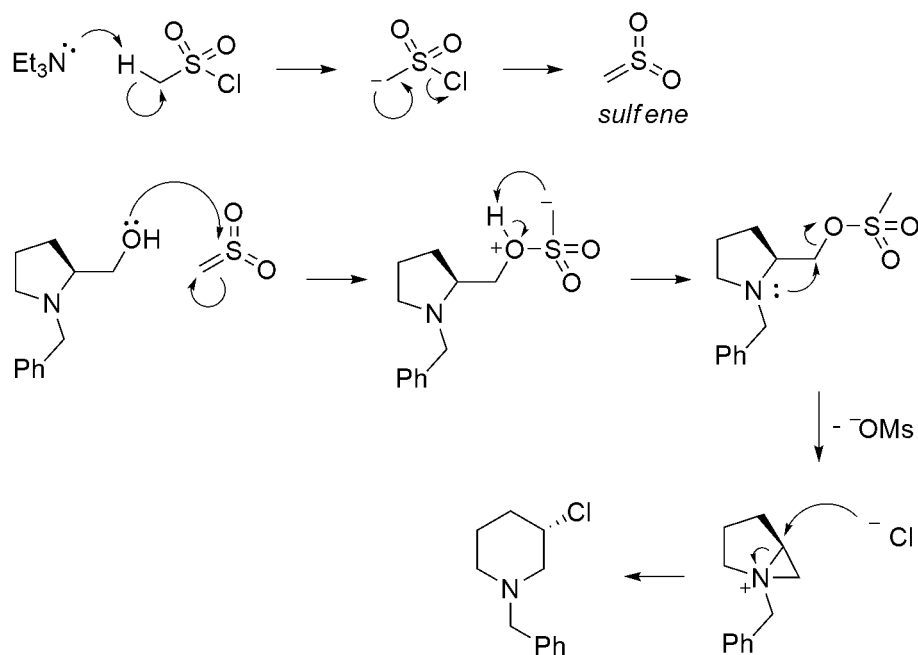
Thus, aminoalcohol **25** was obtained in excellent yield (91 %) by reduction of *L*-proline with LiAlH₄ (**Scheme 12**). Treatment with either benzyl bromide or phenethyl bromide and K₂CO₃ gave the benzyl or homobenzyl protected aminoalcohols **26** and **27** in modest yield (57 % and 48 % respectively). Using a strategy previously reported by Cossy, the aminoalcohols were then converted to β -chloroamines **28** and **29** with simultaneous expansion to the 6-membered ring.¹¹ This transformation proceeds through mesylation of the alcohol, with the nitrogen lone pair then attacking the carbon bearing the mesylate leaving group to give an aziridinium ion. Opening of the aziridinium by chloride leads to the desired six-membered ring with inversion of stereochemistry (**Scheme 13**).

Using conditions previously reported by the Woodward group for the synthesis of enamine *N*-oxides, homobenzyl β -chloroamine **29** was subjected to oxidation with *m*CPBA to quantitatively give β -chloroamine *N*-oxide **30**. The stereochemistry of the *N*-oxide could not be deduced, as the axial and

equatorial protons could not be differentiated from each other by ^1H NMR J values, since these signals were multiplets. This meant that the orientation of the chloride could not be assigned, and an NOE experiment would not reveal which face of the ring the NCH_2 in the homobenzyl chain was closest too. Compound **30** is also an oil, so an X-ray crystal structure could not be obtained.



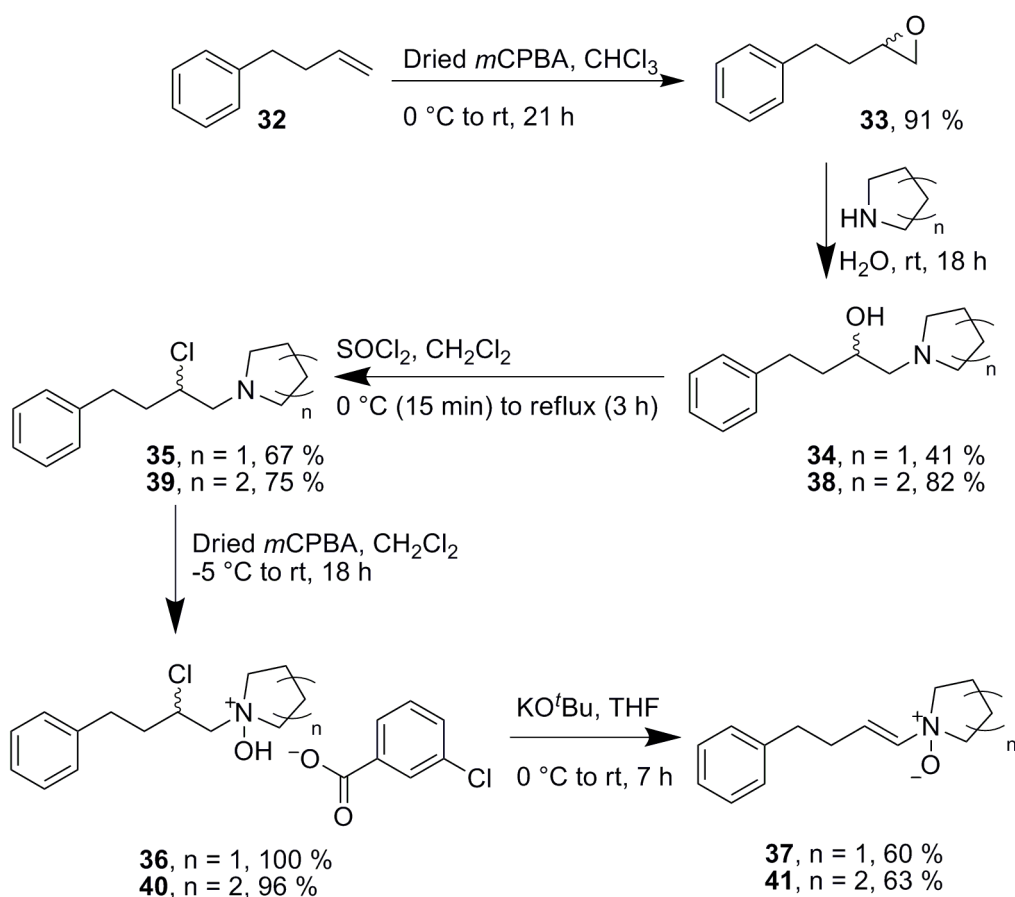
Scheme 12



Again using the Woodward group's existing procedure for generating acyclic enamine *N*-oxides, elimination with potassium *tert*-butoxide failed to give cyclic enamine *N*-oxide **31**. Repeating the oxidation with dried *m*CPBA and distilled solvent, again the oxidation proceeded smoothly but elimination to the enamine *N*-oxide was unsuccessful. A complex mixture was observed by NMR spectroscopy, which could be attributed to competing deprotonation at the benzylic position and elimination to the other side of the chloride.

1.3.2 Synthesis of Acyclic Enamine *N*-oxides

An enamine *N*-oxide which had previously been made in the group was then synthesised (**Scheme 14**). Starting material 4-phenylbut-1-ene **32** was oxidised with *m*CPBA to epoxide **33**, which was opened by attack by pyrrolidine to give aminoalcohol **34**. Treatment with thionyl chloride in CH_2Cl_2 converted the aminoalcohol to the β -chloroamine **35**, which was oxidised with *m*CPBA to yield β -chloroamine *N*-oxide **36** as a *m*-chlorobenzoic acid salt in quantitative yield. Finally, treatment with potassium *tert*-butoxide gave enamine *N*-oxide **37**, with an overall yield of 15 % from the alkene.

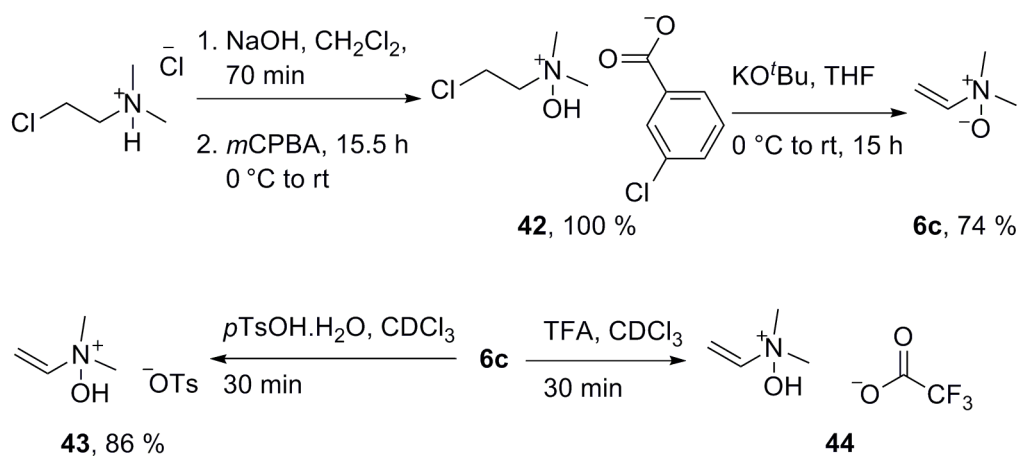


Scheme 14

Similarly, the novel piperidiny enamine *N*-oxide **41** was prepared by the same route. Epoxide **33** was opened by piperidine to give aminoalcohol **38**, (82 %), which was treated with thionyl chloride in CH_2Cl_2 to give β -chloroamine **39**, (75 %). Oxidation with *m*CPBA yielded β -chloroamine *N*-oxide **40** as a *m*-chlorobenzoic acid salt in 96 % yield, and treatment with potassium *tert*-butoxide gave enamine *N*-oxide **41** (63 %).

Another enamine *N*-oxide previously synthesised by the group was also synthesised, namely *N,N*-dimethylvinylamine *N*-oxide **6c** (**Scheme 15**). The group's procedure of treating 2-dimethylaminoethyl chloride·HCl with sodium carbonate in H_2O was found to have isolation problems in my hands, so a modified process of adding sodium hydroxide to a suspension of the hydrochloride salt in CH_2Cl_2 was developed. The free β -chloroamine was not isolated, instead being oxidised with *m*CPBA *in situ* to give a quantitative yield of *N*-(2-chloroethyl)-dimethylamine *N*-oxide (3-chlorobenzoic acid salt) **42**.

Treatment with KO^tBu then gave enamine *N*-oxide **6c** as an oil in 74 % yield.



Scheme 15

In an attempt to generate a solid, crystalline analogue of enamine *N*-oxide **6c**, the crude compound was treated with *p*TsOH·H₂O to give tosic acid salt **43** in 86 % yield. Unfortunately this was also an oil and attempts at recrystallisation were unsuccessful. Similarly trifluoroacetic acid salt **44** was isolated as an oil in quantitative yield, but could not be recrystallised.

1.3.3 Potential Synthetic Routes to Enamine *N*-Oxides

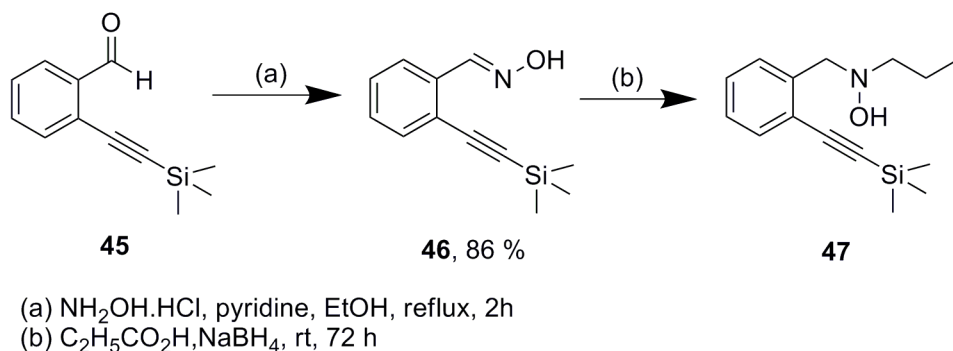
1.3.3.1 Gold-Catalysed Reaction of Alkynes with Hydroxylamines

The reverse Cope cyclisation in which a hydroxylamine and alkene undergo intramolecular reaction to give a cyclic amine *N*-oxide is well documented.¹² It is also known that the addition of nitrogen nucleophiles to alkynes can be catalysed by gold (I) complexes.⁸ With this in mind, the addition of *N,N*-diethylhydroxylamine to phenylacetylene catalysed by 5 mol% Au(I)Cl was attempted at room temperature overnight. However, examination of the crude showed that no enamine *N*-oxide was formed. Previous work in the group had also found difficulty in synthesising enamine *N*-oxides conjugated to a phenyl ring, so choice of substrate may have been the reason for the reaction's failure.

1.3.3.2 Bromine-Activated Reaction of Alkynes with Hydroxylamines

Recently, Ding and Wu reported the electrophilic cyclisation of 2-alkynylbenzaldehyde oximes to generate isoquinoline *N*-oxides.¹³ The electrophile involved was a source of either Br or I, with Br₂ giving the best results in most cases. To test if this methodology could be applied to coupling alkynes and hydroxylamines, *N,N*-diethylhydroxylamine and phenylacetylene were stirred in CH₂Cl₂ and a solution of Br₂ in CH₂Cl₂ was added. Stirring for 24 h at room temperature gave no desired product, but also did not lead to the 1,2-dibromosubstituted alkene from bromination of phenylacetylene. (A control reaction was also run in the absence of hydroxylamine to determine this).

Since the literature precedent involved an intramolecular cyclisation, it was postulated that this may be a requirement for reactivity. Thus 2-ethynylbenzaldehyde oxime **46** was synthesised from the corresponding aldehyde **45** and hydroxylamine hydrochloride in good yield (86 %) (**Scheme 16**), according to Ding and Wu's method. To access the required hydroxylamine **47**, oxime **46** was stirred with sodium borohydride for 72 h in propionic acid. Gribble *et al.* reported these conditions as a means of generating *N,N*-dialkylhydroxylamines from oximes.¹⁴ Upon work-up, however, an insoluble, deep purple polymer formed which could not be taken further.



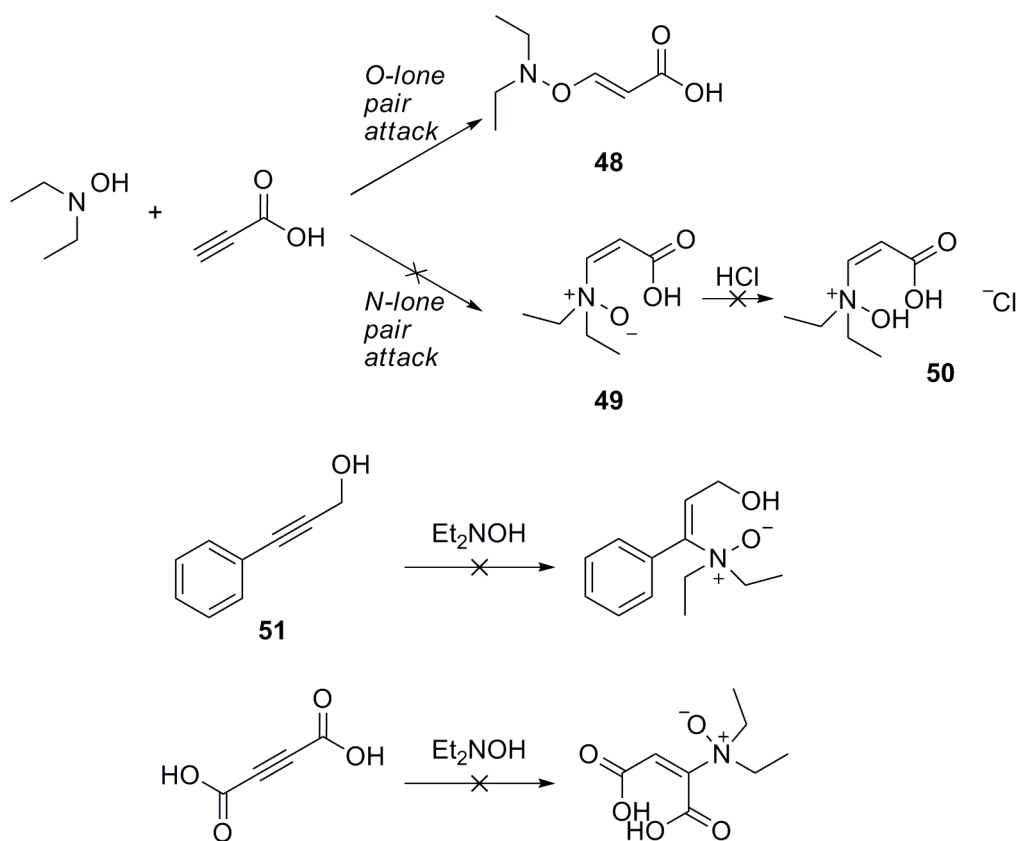
Scheme 16

1.3.3.3 Reaction of Hydroxylamines with Electron-deficient Alkynes

As Winterfeldt and Krohn showed that an enamine *N*-oxide could be synthesised in a single step by reaction of a hydroxylamine with a symmetric electron-deficient alkyne, this idea was applied to unsymmetric alkynes with the aim of expanding the scope of such a transformation.²

Thus, *N,N*-diethylhydroxylamine was reacted with propiolic acid (**Scheme 17**). After 21 h at room temperature in CDCl₃, a *ca.* 13:1 mixture of *O*-attack product **48** and a second alkene-containing product, potentially desired *N*-attack product **49**, was observed by ¹H NMR spectroscopy, with unreacted starting material still present. Product **48** was assigned as its (*E*)-isomer, with a pair of doublets at chemical shifts of 7.79 and 5.50 with a coupling constant of 12.6 Hz for the alkene protons being consistent with data for the corresponding (*E*)-methyl ester previously synthesised in the Woodward group (1H doublets at 7.68 and 5.47 ppm with *J* = 12.4 Hz).¹⁵ The other alkene-containing product was identified by ¹H doublet signals at chemical shifts of 6.83 and 6.71 ppm (*J* = 13.3 Hz).

In a bid to prevent reaction at the *O*-terminus of the hydroxylamine, and favour that at the *N*-terminus, the reaction was carried out with dropwise addition of propiolic acid to a stirred solution of hydroxylamine in chloroform at 0 °C. Unfortunately, stirring at this temperature for a length of time from 5 to 90 min, before quenching with 2 M HCl_(aq) to trap any enamine *N*-oxide as its hydrochloride salt **50**, also failed to yield the desired product. In each case, only the undesired product **48** and in some cases protonated hydroxylamine was observed. Reaction in acetic acid also resulted in formation of **48** with full consumption of propiolic acid after 5 min.



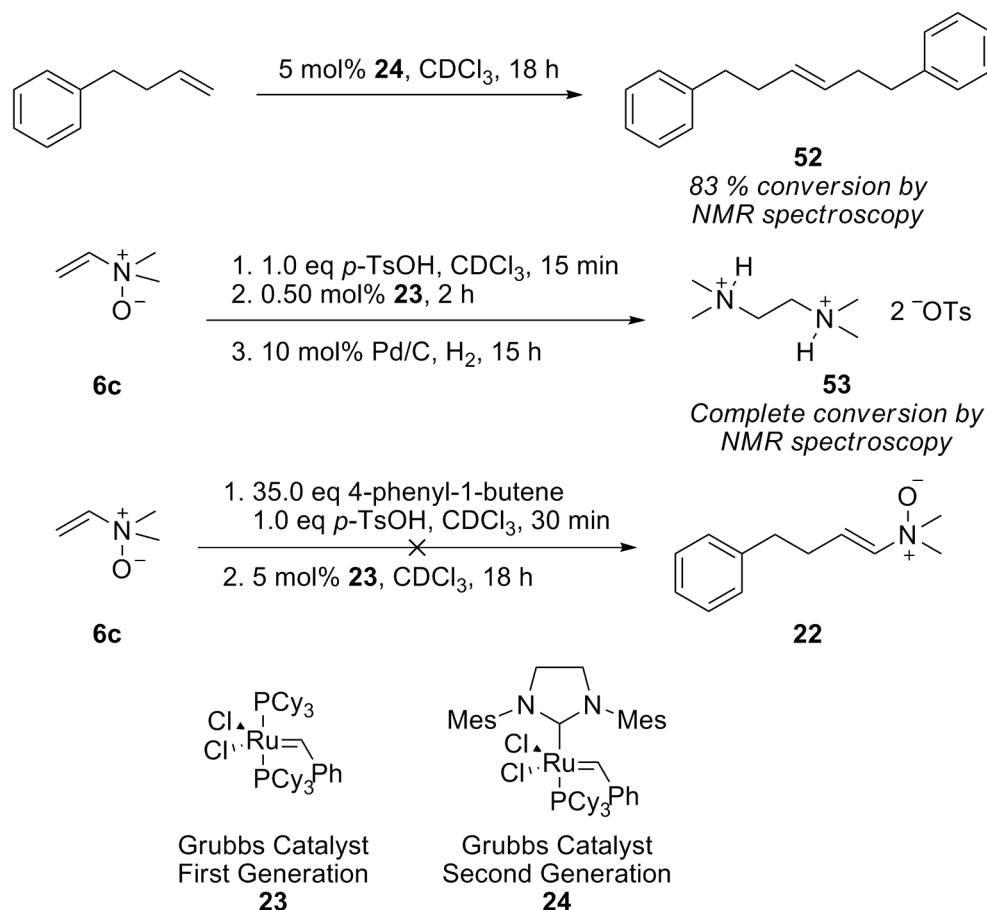
Scheme 17

To examine the effect on reactivity of the carbonyl in the alkynyl compound, propargylic alcohol **51** was also reacted with the hydroxylamine, with no reaction observed by NMR spectroscopy after 21 h at room temperature in CDCl_3 . While it is difficult to propose a mechanism for reaction between Et_2NOH and **51**, this experiment showed that electron-withdrawing substituents on the alkyne are necessary for reaction to occur. The attempted reaction of *N,N*-diethylhydroxylamine with doubly-activated acetylenedicarboxylic acid in MeOD generated a complex mixture after monitoring by NMR spectroscopy over 2 days.

1.3.3.4 Development of Cross Metathesis Methodology

Another attempt at a one-step synthesis of enamine *N*-oxides was made by employing cross metathesis of simple enamine *N*-oxide **6c** and alkene **32** (**Scheme 11**). Initially, the conditions required to give the homocoupling product of each component were studied (**Scheme 18**). Concerning the alkene

homocouple **52**, it was found that when Grubbs first generation catalyst **23** was employed, 15 mol% of the catalyst was required to drive the reaction to completion after catalyst deactivation occurred with two successive additions of 5 mol% each. Using 5 mol% Grubbs second generation catalyst **24**, NMR spectroscopy showed that 83 % conversion to homocouple **52** was achieved before catalyst deactivation after 18 h stirring in CDCl₃.



Scheme 18

In order to study the homocoupling of enamine *N*-oxide **6c**, the *N*-oxide was protected as its tosic acid salt to prevent potential reaction with the Grubbs catalyst. This strategy has been reported for substrates with Lewis basic sites, which can displace phosphine ligands, leading to poisoning of the catalyst.¹⁶ Reaction with Grubbs first generation catalyst to give **53** was found to occur within 2 h even when the catalyst loading was reduced to 0.5 mol%. This disparity in the reaction rates of the homocoupling reactions meant that cross coupling was unlikely, as homocoupling of the enamine *N*-oxide would

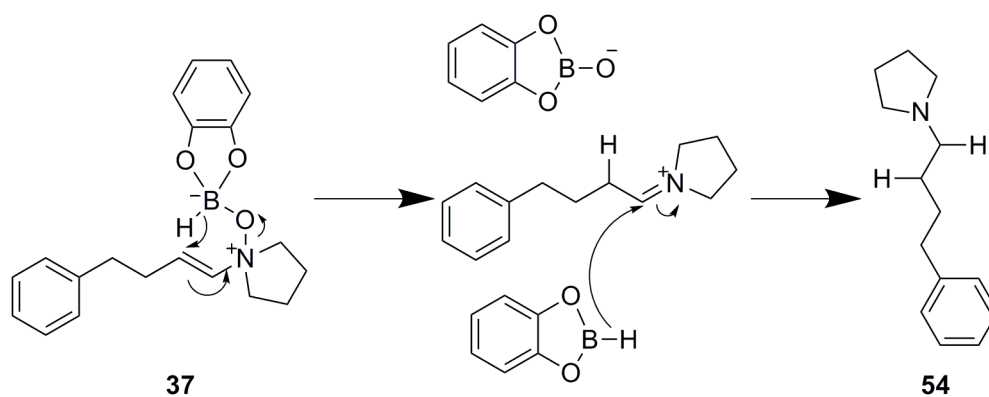
dominate before cross-coupling could occur.

This was borne out when cross-coupling was investigated. Using an excess of alkene **32**, 5 mol% Grubbs first generation catalyst and one equivalent of tosic acid to protect the *N*-oxide, the alkene was found not to react whilst the enamine *N*-oxide was converted to a complex mixture. Reducing the excess and changing to Grubbs second generation catalyst, with subsequent hydrogenation also failed to yield any product.

1.3.4 Reactions of Enamine *N*-Oxides

1.3.4.1 Reaction with Organoboron Reagents

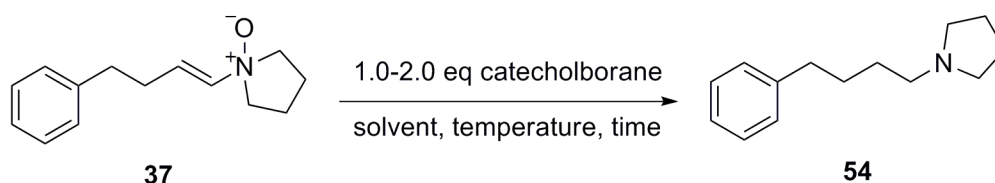
In order to facilitate the loss of O^- from enamine *N*-oxides during iminium ion formation, it was felt desirable to use nucleophiles, which, once reacted, would generate a species that would form a strong bond to oxygen. Catecholborane was selected as such a reagent, which could coordinate to the *N*-oxide, delivering a hydride to the enamine *N*-oxide double bond and generating an iminium species by subsequent loss of the borate species (**Scheme 19**). Attack on the iminium by a second equivalent of catecholborane would then lead to amine **54**.



Scheme 19

Enamine *N*-oxide **37** was treated with catecholborane (1.0 to 2.0 eq) under a range of conditions (**Scheme 20**, **Table 1**). Initial experiments at 70 °C

resulted in lower yields of amine **54** than were achieved at room temperature. Addition of catecholborane at $-40\text{ }^{\circ}\text{C}$ gave a lower yield than room temperature addition. Basic work-up using NaOH also gave higher yields than oxidative work up (H_2O_2), presumably aiding removal of catechol into the aqueous phase by deprotonation to catecholate. Toluene was found to be the most suitable solvent; the enamine *N*-oxide was readily soluble, and *N,N*-dimethylformamide was difficult to remove from the product. Two equivalents of catecholborane were essential in giving a synthetically useful yield. Overall, the optimised conditions found were to use two equivalents of catecholborane, stirring for 18 h at room temperature in toluene, with NaOH work-up (entry **7**). Amine **54** was obtained in 78 % yield under these conditions.



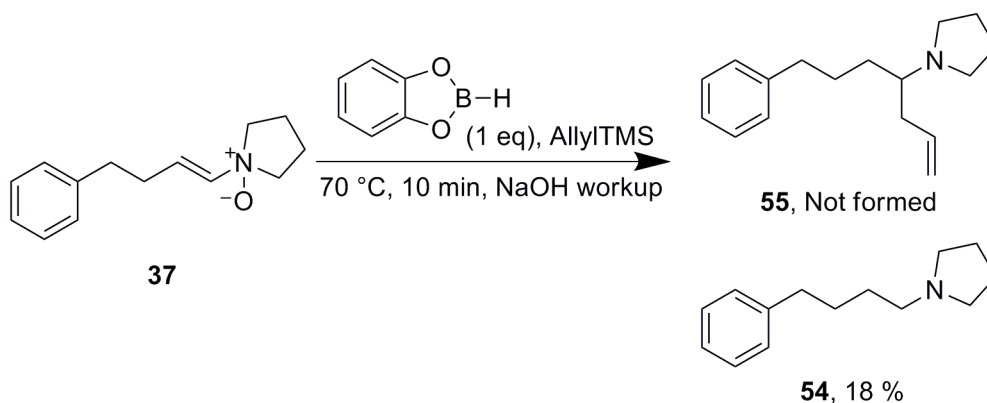
Scheme 20

Entry	eq CatBH	Solvent	T ($^{\circ}\text{C}$)	Time	Work-up	Yield (%) ^a
1	2.0	Toluene	70	19 h	NaOH	0
2	1.0	Toluene	70	10 min	NaOH	13
3	1.0	Toluene	70	10 min	H_2O_2	8
4	2.0	Toluene	70	19 h	H_2O_2	8
5	1.0	Toluene	rt	18 h	NaOH	38
6	1.0	DMF	rt	18 h	NaOH	12
7	2.0	Toluene	rt	18 h	NaOH	78
8	2.0	Toluene	-40 to rt	24 h	NaOH	40

^a Isolated yield.

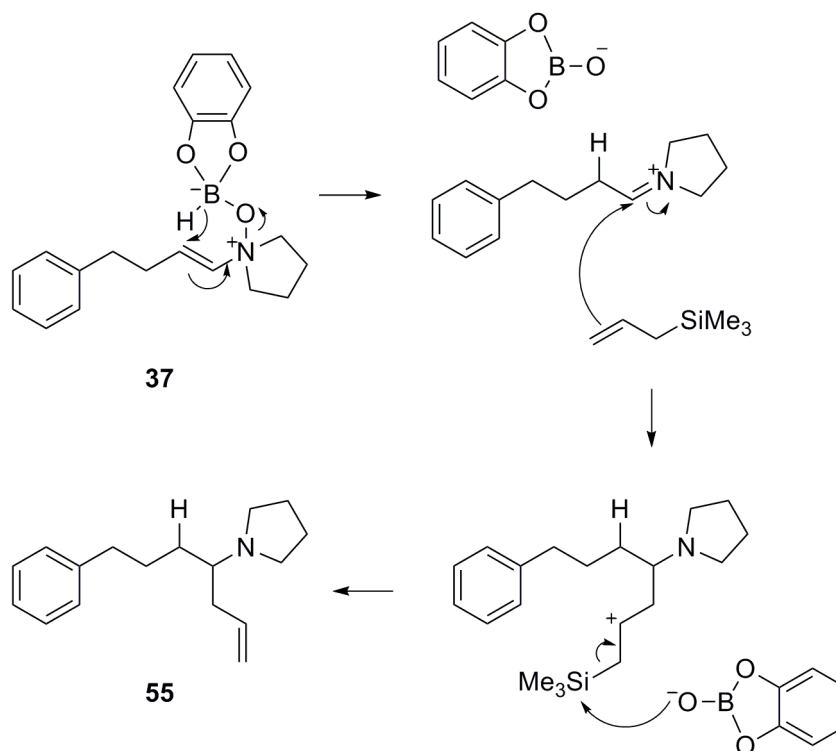
Table 1

That amine **54** was isolated as the major product from this reaction is a clear proof of concept for the Umpolung process, and the mechanism proposed in **Scheme 19**. However, addition of hydrogen at the alkene is not particularly synthetically useful. To extend this to different nucleophiles, the reaction was also run using allyltrimethylsilane as the solvent, in an attempt to intercept the iminium species with an allyl anion, to give α -allyl-substituted amine **55** (**Scheme 21**). It was envisaged that with a large excess of allyltrimethylsilane present, the iminium species would be attacked by the allylsilane, with subsequent nucleophilic substitution at silicon by the outgoing borate species giving the desired homoallylamine (**Scheme 22**).



Scheme 21

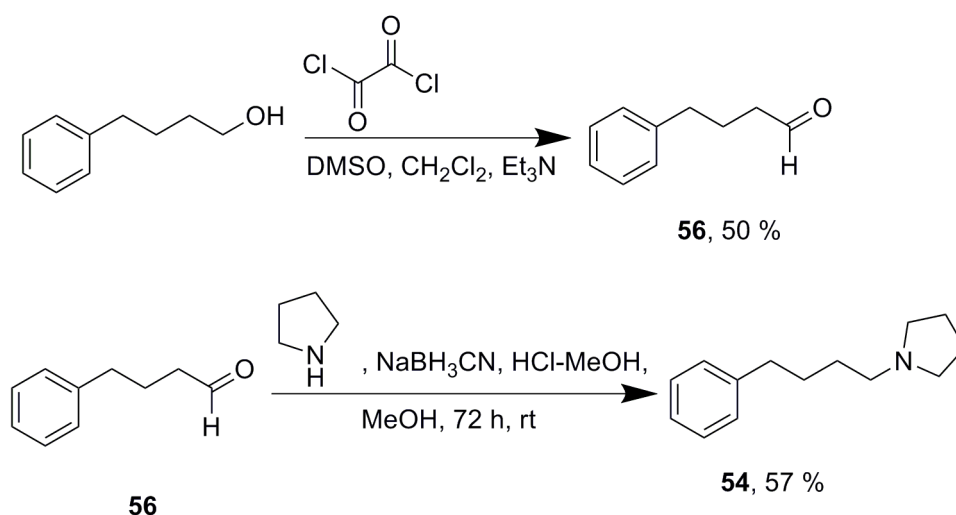
This was unsuccessful, giving a small amount (18 %) of amine **54**, but was not run under optimised conditions. The formation of amine **54** can be accounted for by the mechanism in **Scheme 19**, with interception of the iminium species by a second catecholborane molecule, with a slightly higher yield than observed under similar conditions in toluene (**Table 1**, entry 2).



Scheme 22

1.3.4.2 Amine Synthesis by an Alternative Route for Structural Comparison

Given that amine **54** is a novel compound, the synthesis of the same compound by an alternative route using existing methodology was carried out, in order to compare the spectroscopic data obtained in each case and confirm the structural assignment from the reaction of catecholborane and enamine *N*-oxide **37**. Thus, aldehyde **56** was synthesised in 50 % yield without any overoxidation using Swern oxidation of 4-phenyl-1-butanol (**Scheme 23**).^{17,18} Reductive amination of the aldehyde with sodium cyanoborohydride and pyrrolidine then gave amine **54** in 57 % yield.¹⁹



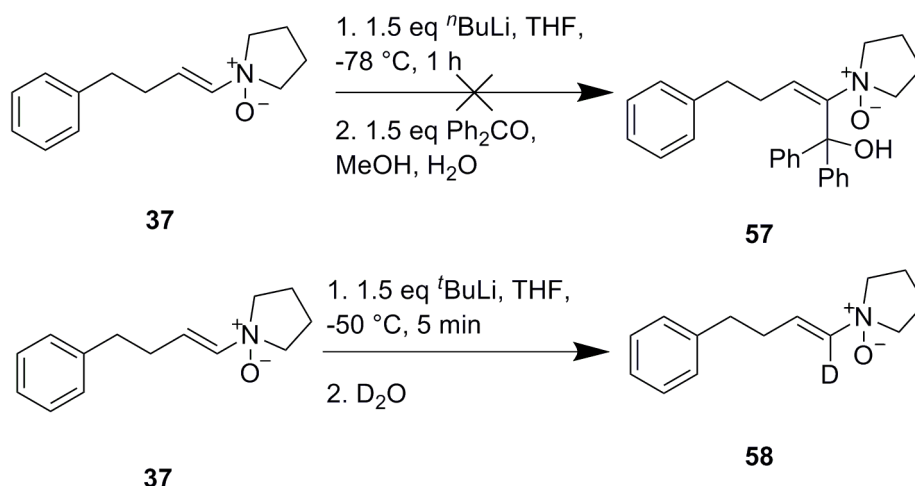
Scheme 23

Comparing the spectral data for amine **54** derived by the two different routes from enamine *N*-oxide or alcohol, interestingly there are some differences. While both have identical IR spectra, and the HRMS spectra both feature the correct molecular ion at m/z 203, there is also an additional signal at m/z 214 in that of the enamine *N*-oxide derived sample. In addition, the ^1H and ^{13}C NMR spectra exhibit different chemical shifts for the protons or carbons next to nitrogen. DEPT experiments have confirmed that in both cases all the aliphatic carbon environments are CH_2 , and it seems likely that the structure of the amine is the same for both routes, and that the sample derived from enamine *N*-oxide **37** has formed a triaminoborane species, observed in the mass spectrum as free amine and the amine coordinated to boron (calculated m/z 214.1767, found m/z 214.1773).

1.3.4.3 α -Deprotonation with Alkylolithium Bases

Given the O'Neil group's report of α -lithiation of quinuclidine-derived enamine *N*-oxide **11a** and subsequent trapping with electrophiles (**Scheme 5**), application of this methodology to our enamine *N*-oxides was of interest.⁵ While O'Neil's procedure uses $t\text{BuLi}$, we initially attempted lithiation with the milder $n\text{BuLi}$ to ascertain the strength of base required to deprotonate at the α -position (**Scheme 24**). Treatment of enamine *N*-oxide **37** with 1.5 eq $n\text{BuLi}$ in THF at -78°C for 1 h, followed by trapping with benzophenone failed to

give any α -deprotonation product **57** with only starting material being recovered. The same result was observed after extending lithiation reaction time to 3 h, indicating that n BuLi is not a strong enough base to deprotonate the enamine *N*-oxide.

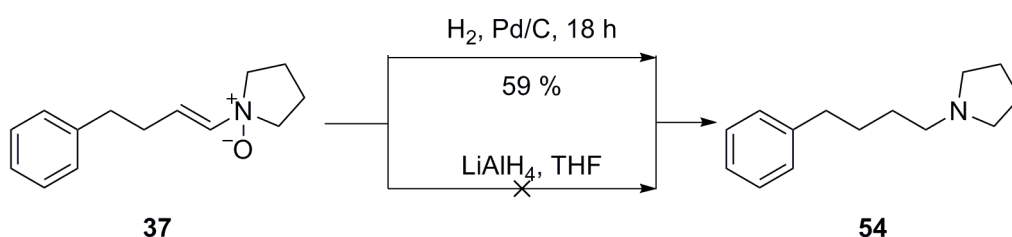


Scheme 24

Use of t BuLi was fortunately more successful. When treated with 1.5 eq t BuLi in THF at $-50\text{ }^{\circ}\text{C}$, enamine *N*-oxide **37** was completely deprotonated at the α -alkene position after a reaction time of only 5 min. Subsequent deuterium incorporation was also achieved by adding 0.1 mL D_2O , giving deuterio-enamine *N*-oxide **58**. As an extension of this, treatment of **37** with t BuLi as above but with a 15 min reaction time to fully ensure complete deprotonation, followed by addition of an electrophile (benzaldehyde, cyclohexanone or benzonitrile), was carried out. Unfortunately none of these reactions were successful. These results contrast with those reported by O'Neil for the quinuclidine-derived enamine *N*-oxide, with successful addition to benzaldehyde reported in 78 % yield. A possible explanation for this could be the increased steric encumbrance of *trans* enamine *N*-oxide **37** compared to the *cis* arrangement of **11a**. Enamine *N*-oxide **6c** was also treated with t BuLi at $-50\text{ }^{\circ}\text{C}$ before trapping with iodine. Unfortunately, even with 2 h reaction time with the base, only starting material was obtained.

1.3.4.4 Selectivity of Reduction of Enamine *N*-Oxides

The effect of different reducing agents on enamine *N*-oxides was investigated. Reaction of enamine *N*-oxide **37** with 10 mol% of 5 % Pd on C under H₂ for 18 h saw reduction of both the alkene and *N*-oxide to afford amine **54** in 59 % yield, with no selective reduction of either moiety observed (**Scheme 25**). Conversely, reduction with LiAlH₄ left the enamine *N*-oxide untouched.

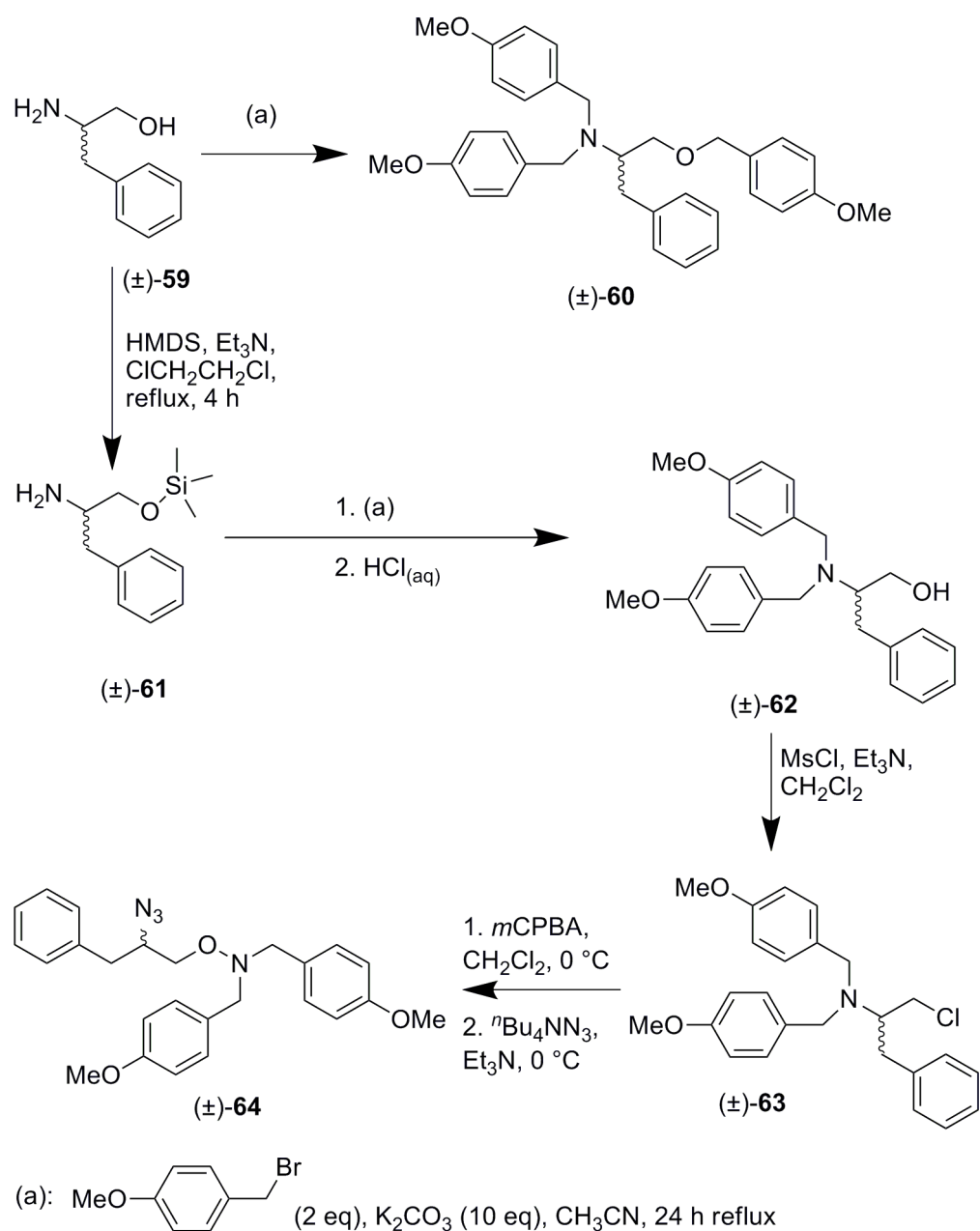


Scheme 25

1.3.5 Investigations into the Owari Rearrangement

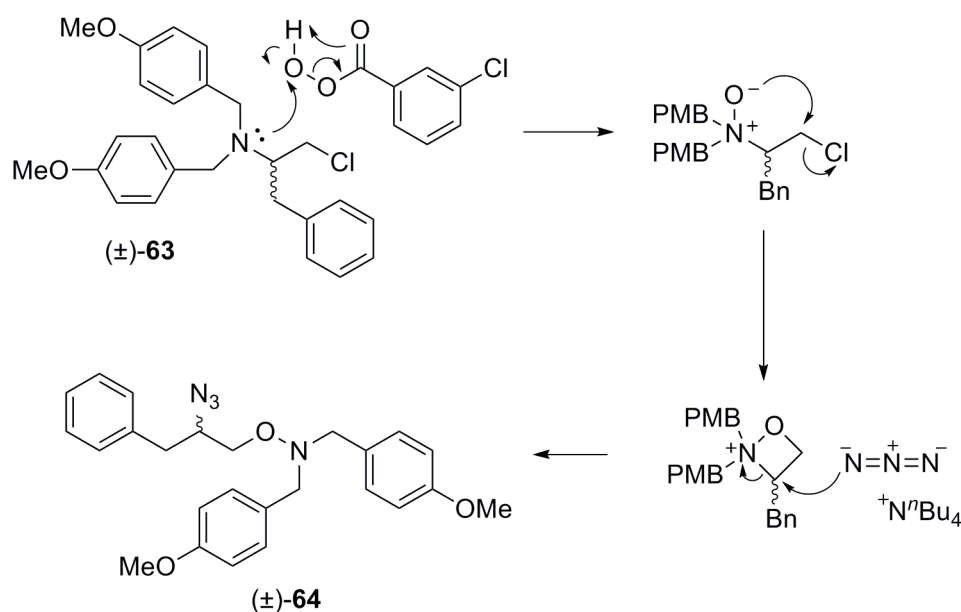
To obtain a substrate for the Owari rearrangement, aminoalcohol (±)-**59** was *N*-protected by treatment with two equivalents of *p*-methoxybenzyl bromide and ten equivalents of potassium carbonate (**Scheme 26**). Unfortunately NMR spectroscopy and MS revealed the product to be *O*-protected as well as doubly *N*-protected, namely aminoalcohol (±)-**60**, obtained in 33 % yield.

To overcome this, the hydroxyl group of (±)-**59** was first converted to silyl ether (±)-**61** using hexamethyldisilazane and triethylamine at reflux in 1,2-dichloroethane for 4 h.²⁰ Treatment of the crude silyl ether with *p*-methoxybenzyl bromide and potassium carbonate as before, followed by washing with 2 M HCl_(aq) to cleave the silyl protecting group yielded the desired *N*-protected aminoalcohol (±)-**62** (64 %). Reaction with MsCl and triethylamine in CH₂Cl₂ then gave β-chloroamine (±)-**63** in 32 % yield.



Scheme 26

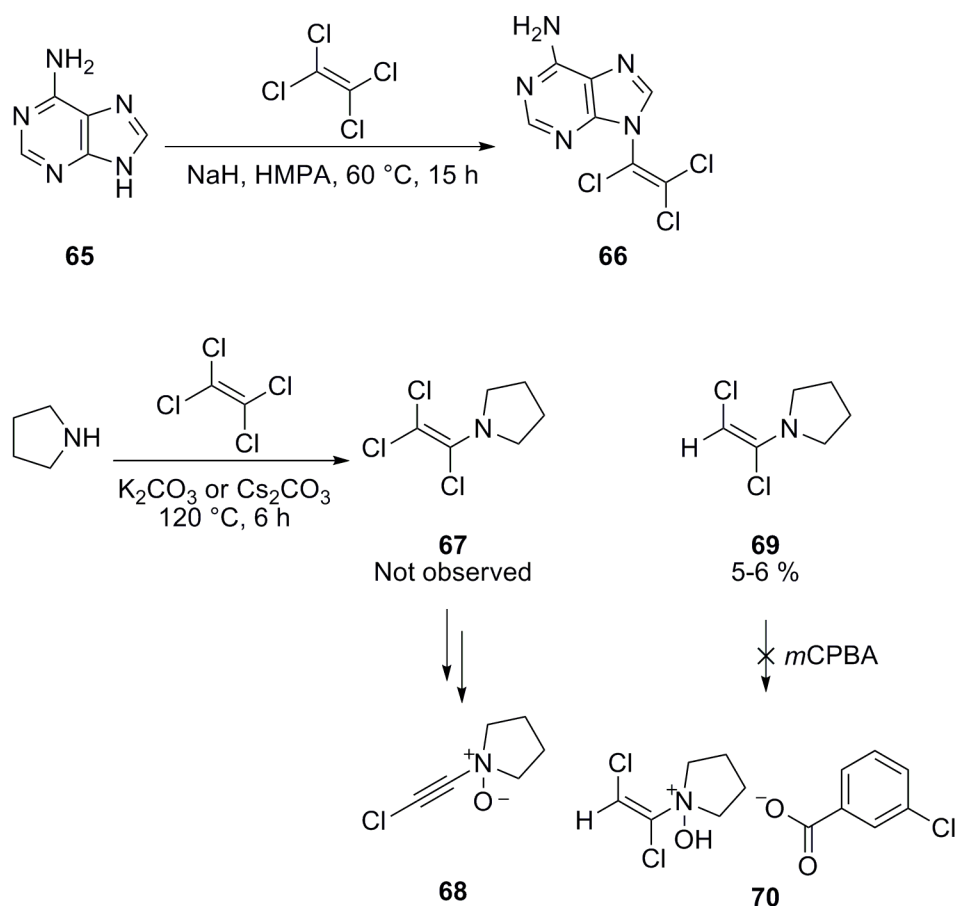
With the β -chloroamine in hand, Owari rearrangement product $(\pm)\text{-64}$ was obtained by *N*-oxidation with *m*CPBA, followed by substitution of chloride by the *N*-oxide, and opening of the oxazetidinium species thus formed by tetrabutylammonium azide (**Scheme 27**). However, it was not possible to separate the product from *ca.* 0.3 eq *m*-chlorobenzoic acid by flash column chromatography.



Scheme 27

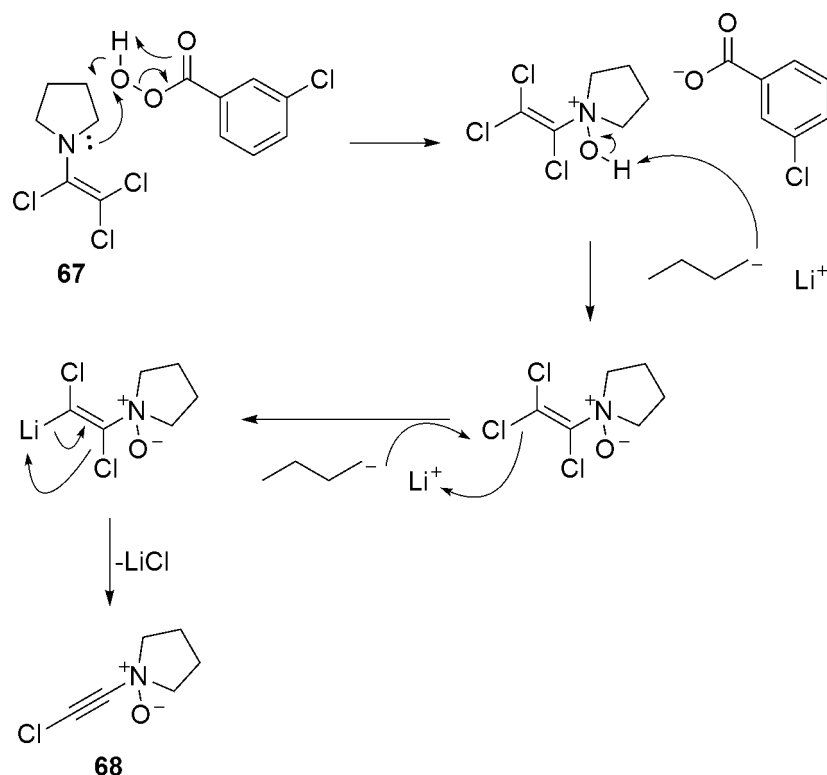
1.3.6 Synthesis of Ynamine and Ynamine *N*-oxide Precursors

With a view to synthesising novel ynamine *N*-oxide **68**, the reaction of tetrachloroethylene with pyrrolidine to give trichloroenamine **67** was studied (**Scheme 28**). This transformation has some precedent in the literature, where Zemlicka and coworkers report the treatment of tetrachloroethylene and purine **65** with NaH and HMPA to give chloroenamine **66**.²¹ Initial reactions carried out by heating a neat mixture of pyrrolidine and tetrachloroethylene in the presence of K_2CO_3 at 120 °C for 2-15 h or 80 °C for 17 h failed to isolate any product. Running the reaction in the absence of base was also unsuccessful. However, on switching to Cs_2CO_3 and pre-drying the amine, heating the neat mixture at 120 °C for 6 h resulted in 5 % of dichloroenamine **69** (the geometric configuration about the alkene could not be established). A similar result was obtained using K_2CO_3 in combination with the pre-dried amine (6 % **69**).



Scheme 28

Synthesis of ynamine *N*-oxide **68** was intended to proceed *via* the *N*-oxidation of trichloroenamine **67** with *m*CPBA, followed by elimination of chlorine across the double bond (**Scheme 29**). Generation of ynamines by elimination of Cl₂ from di- and trichloroenamines using ^{*n*}BuLi has been reported.²² A modified version of this, with an extra equivalent of ^{*n*}BuLi required to first deprotonate the N-OH could have been trialed as a means to access **68**. In an effort to see if dichloroenamine **69** could be oxidised to its *N*-oxide 3-chlorobenzoic acid salt **70**, a crude sample of **69** was treated with *m*CPBA under argon at 0 °C and allowed to come to room temperature for 22 h. Unfortunately, reaction failed to occur.



Scheme 29

1.4 Conclusions

The study of enamine *N*-oxides met with mixed success, which is only to be expected given the dearth of knowledge of their chemistry. Fortunately there have been some moderate successes which lay the foundations for future work. On the other hand there have been many reactions which simply did not work, which are also helpful in learning about these compounds.

First of all, it has been shown that using enamine *N*-oxides to generate electrophilic intermediates in an Umpolung approach to existing chemistry is possible. Treatment of an enamine *N*-oxide with catecholborane leads to addition of hydrogen across the double bond with oxygen abstraction, a process which it is difficult to envisage proceeding unless by generation of an iminium and subsequent reaction *via* the proposed Umpolung mechanism. It must be noted that so far no other nucleophiles have been successfully added by this type of reaction, and more work is needed to be able to do this.

Another important success was the deprotonation of enamine *N*-oxides. Treatment with ^tBuLi gave complete α -deprotonation after just five minutes, allowing deuterium incorporation on washing with D₂O. It was found that ⁿBuLi was not a strong enough base to accomplish this, leaving the starting enamine *N*-oxide unaffected after 3 h reaction time. This approach has great potential to introduce interesting functionality and chirality at the α -position, but so far no other electrophiles have successfully been added. As regards the selectivity of enamine *N*-oxide reduction, it was found that treatment with H₂ and Pd on charcoal led to reduction of both the alkene and *N*-oxide, whilst treatment with LiAlH₄ left the enamine *N*-oxide unchanged.

Unfortunately, the attempted one-step synthesis of enamine *N*-oxides from hydroxylamines and alkynes was not successful. Neither the activation of the alkyne by gold (I) chloride or by bromine has led to enamine *N*-oxides. Further investigation into intramolecular cyclisation using bromine was hampered by an inability to obtain the starting alkynyl hydroxylamine. Cross metathesis also failed to yield access to the desired enamine *N*-oxides due to a mismatch of homocoupling rates for the alkene and enamine *N*-oxide starting materials.

Synthesis of enamine *N*-oxides by the existing Woodward group route has allowed an additional novel acyclic compound to be obtained with good yields, but synthesis of a cyclic enamine *N*-oxide was unsuccessful, potentially due to competing benzylic deprotonation and elimination processes.

Although there has not been much work on the synthetic utility of the Owari rearrangement, the ability to protect the hydroxyl group of aminoalcohols with silyl ethers, prior to *N*-protection with *para*-methoxybenzyl groups, and subsequent cleavage in mild acid, is a potentially useful approach. Furthermore rearrangement to an azide was successful, albeit with purification problems.

1.5 Future Studies

Given the difficulties encountered with this chemistry, it is difficult to see clear areas for further work. Having found that ^tBuLi is a suitable base for

α -deprotonation, reactions using sub-stoichiometric amounts of chiral bases, in conjunction with stoichiometric quantities of achiral reagents could also be investigated as a means of achieving stereocontrol.

Regarding the Umpolung reactivity of enamine *N*-oxides, the successful proof of concept with catecholborane could be built upon by using different organoboron reagents to install more useful substituents onto the amines generated. Aryl boranes, such as triphenyl boron, have a B-C bond strength similar to the B-H bond strength in catecholborane. It is possible that these may therefore react similarly to catecholborane with enamine *N*-oxides. Allylboranes may also be useful. Brown has shown that asymmetric allylboration using chiral allylboron reagents such as allyldiisopinocampheylboranes can achieve high enantiomeric excess.^{23,24} Allyl substituents could also be used to create cyclic structures *via* ring-closing metathesis. Other allyl-metal reagents that could be investigated include allyl zinc bromide and allyl indium compounds.

Further work on a one-step approach to enamine *N*-oxides could look at more active gold catalysts such as the combination of triphenylphosphine, AuCl and silver triflate. Alternatively different metals could be employed in catalysis. Similar reactions catalysed by silver triflate itself or iridium hydrides have been reported.^{25,26}

CHAPTER 2

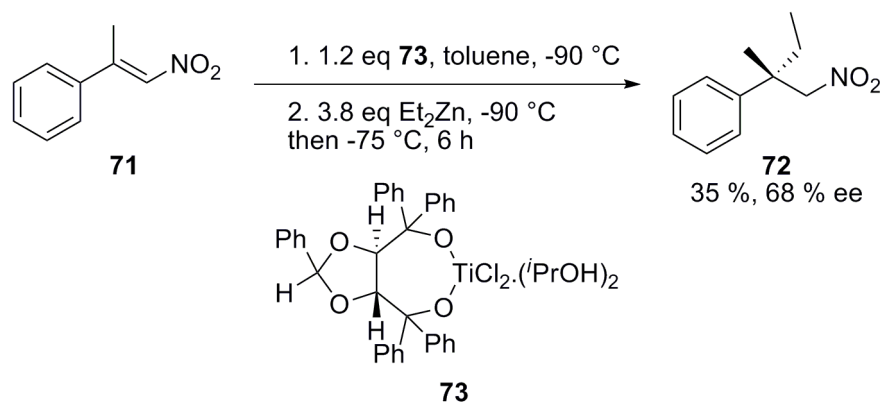
Asymmetric Conjugate Addition Reactions

2.1 Conjugate Addition to Nitroalkenes

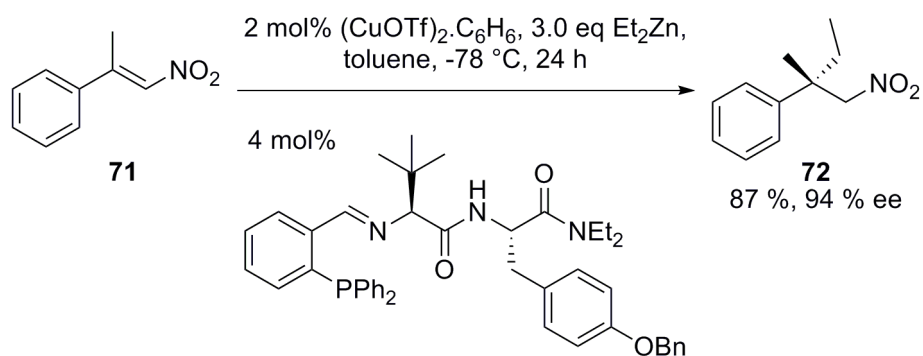
2.1.1 Introduction

Asymmetric conjugate addition reactions are a powerful means of introducing chirality and carbon-carbon bonds. While this area has been widely explored, particularly with copper catalysts, there are still challenging and underdeveloped aspects of this methodology. Conjugate addition to trisubstituted nitroalkenes to furnish nitroalkanes with a quaternary chiral centre is an example of this. Nitroalkanes are useful synthetic intermediates which can undergo transformation to amines, carboxylic acids, aldehydes and alkanes and alkenes *via* denitration.^{27,28}

Only a handful of procedures for asymmetric conjugate addition to β,β -disubstituted nitroalkenes have been reported in the literature. Seebach and Schäfer have used a chiral, Lewis-acidic titanium TADDOLate species **73** in the enantioselective addition of diethylzinc to nitroalkene **71** to generate the quaternary centre in nitroalkane **72**, albeit with lower yield and enantioselectivity than additions to β -monosubstituted nitroalkenes under the same conditions (**Scheme 30**).²⁹ In 2005, Hoveyda reported the first catalytic asymmetric addition of diethylzinc to nitroalkene **71** using a peptide ligand to give **72** with high enantioselectivity (up to 94 % ee) in moderate to good yield (**Scheme 31**).³⁰

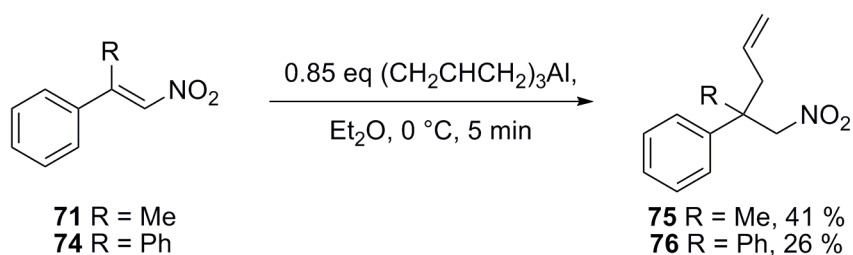


Scheme 30



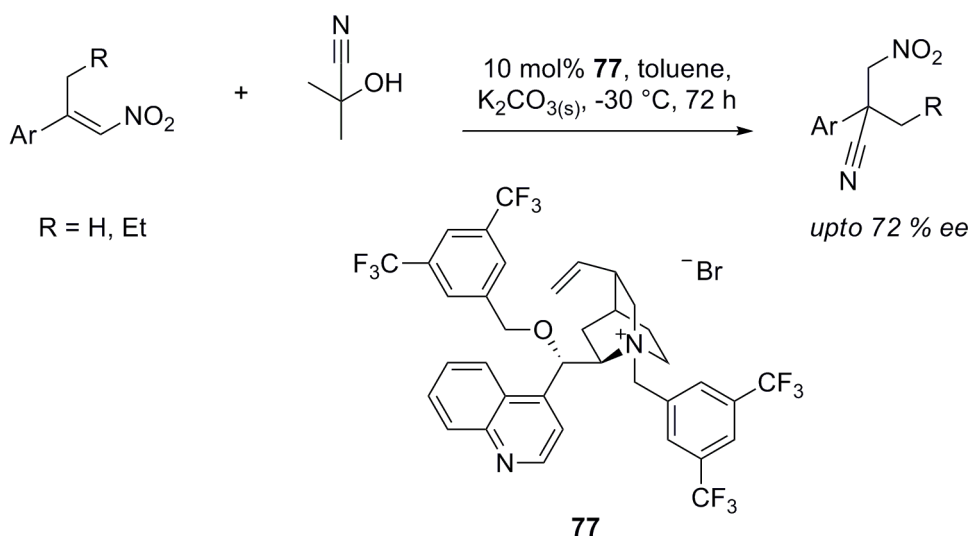
Scheme 31

Conjugate addition of organoaluminium reagents to β,β -disubstituted nitroalkenes to give racemic products has also been reported. Yao and co-workers obtained nitroalkene **75** bearing an all-carbon quaternary centre upon reaction of triallylaluminium with nitroalkene **71**, while reaction with diphenyl nitroalkene **74** led to product **76** (**Scheme 32**).³¹ Low yields of **75** (41 %) and **76** (26 %) were again observed due to the steric hindrance of the starting nitroalkenes.

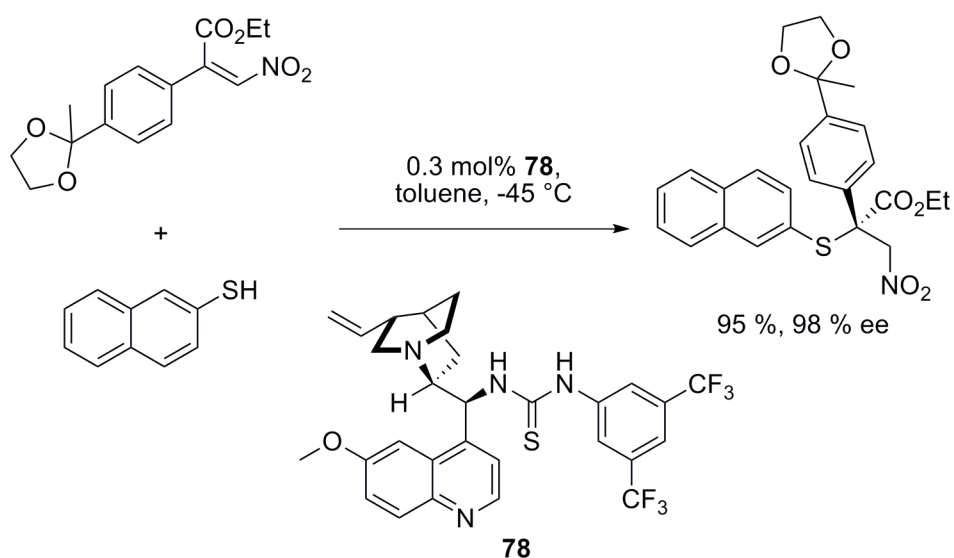


Scheme 32

Enantioselective 1,4-additions of thiols and cyanohydrins have also been developed. In 2008, Fochi and Ricci reported the use of phase transfer catalyst **77** in an enantioselective conjugate addition of cyanide generated from acetone cyanohydrin to β,β -disubstituted nitroalkenes with upto 72 % ee (**Scheme 33**).³² Although not resulting in formation of all-carbon quaternary centres, the Xiao group have developed an asymmetric organocatalytic 1,4-addition of thiols to nitroacrylates to give nitroalkanes bearing a hetero-quaternary stereogenic centre with upto 98 % ee (**Scheme 34**).³³

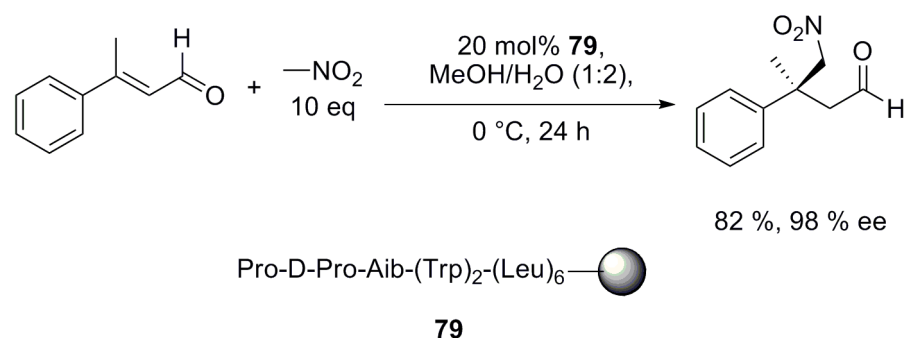


Scheme 33



Scheme 34

An alternative approach to the synthesis of chiral nitroalkanes involves the asymmetric conjugate addition of nitroalkanes to enals (**Scheme 35**).³⁴ Recently, Kudo and Akagawa reported the use of resin-supported peptide catalyst **79** in the enantioselective 1,4-addition of nitromethane to β,β -disubstituted enals, giving good yields and excellent ee.



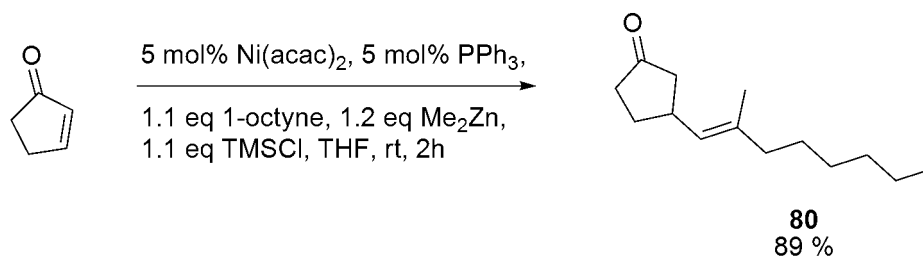
Scheme 35

2.1.2 Aims and Objectives

Following the lack of success in enamine *N*-oxide chemistry, the development of asymmetric conjugate addition reactions became a main objective. The enantioselective generation of quaternary stereocentres by conjugate addition onto nitroalkenes remains a challenge in synthetic chemistry. More readily available or easily accessible routes than Hoveyda's reported catalytic approach using a peptide-based ligand would be desirable.³⁰

The initial objective was to investigate copper-catalysed asymmetric conjugate addition of alkyl organometallics to tri-substituted nitroalkenes to give an all-carbon quaternary chiral centre. Due to problems in analysing reaction products by chiral gas chromatography, simpler asymmetric conjugate addition reactions were chosen as areas for development. Hence the copper-catalysed asymmetric conjugate addition of methyl organometallics to nitrostyrene was studied with the objective of finding suitable conditions for application to more complex systems.

Nickel-catalysed processes were also of interest. For instance, Ikeda reported the tandem coupling of an enone with dimethylzinc, TMSCl, and alkyne to give products such as **80** (**Scheme 36**), and one of our aims was to investigate the applicability of this process to nitroalkenes.³⁵

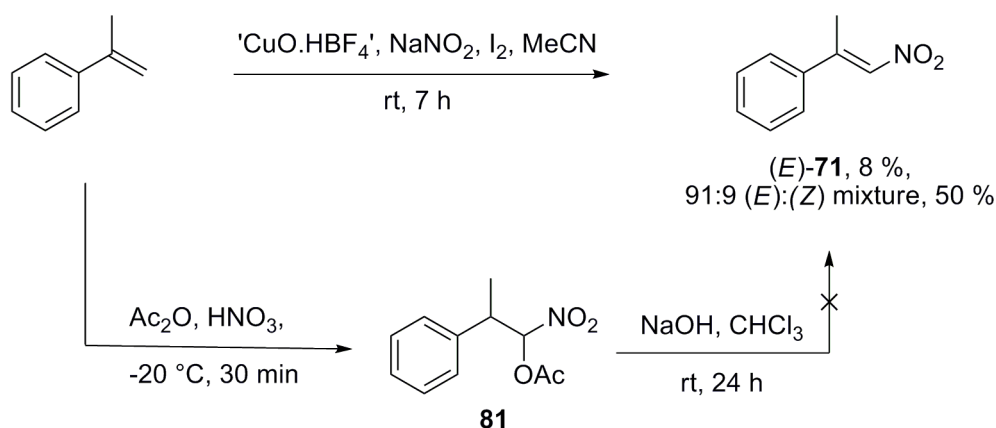


Scheme 36

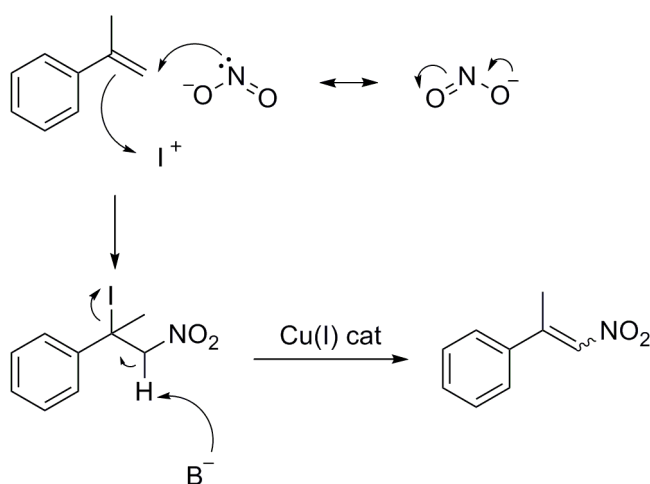
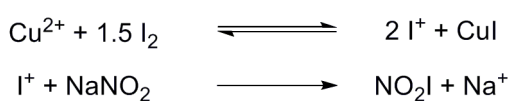
2.1.3 Results and Discussion

2.1.3.1 Conjugate Addition of Alkyl- and Vinylaluminium Species to Nitroalkenes

The enantioselective generation of quaternary chiral centres by conjugate addition to nitroalkenes remains a challenge in synthesis. In order to generate a quaternary chiral centre, it is necessary to use a trisubstituted nitroalkene. To this end, (*E*)-1-nitro-2-phenylpropene **71** was selected as a suitable substrate. Utilising a procedure reported by Campos, α -methylstyrene was reacted with sodium nitrite, iodine and preformed ' $\text{CuO} \cdot \text{HBF}_4$ ' in acetonitrile to give nitroalkene (*E*)-**71** in only 8 % yield, with 50 % of a 10.5:1 mixture of (*E*)-**71** and (*Z*)-**71** (Scheme 37).³⁶ A low concentration of I^+ is present in an equilibrium with iodine and Cu^{2+} . The I^+ is believed to react with sodium nitrite to form NO_2I , which attacks the C-C double bond. The resulting (2-iodo-1-nitropropan-2-yl)benzene leads directly to the nitroalkene by dehydro-iodination, believed to be catalysed by copper(I) salts generated in the reaction (Scheme 38).



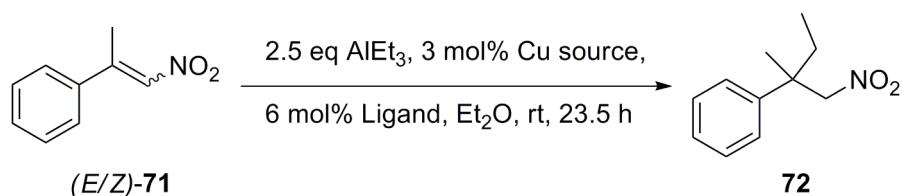
Scheme 37



Scheme 38

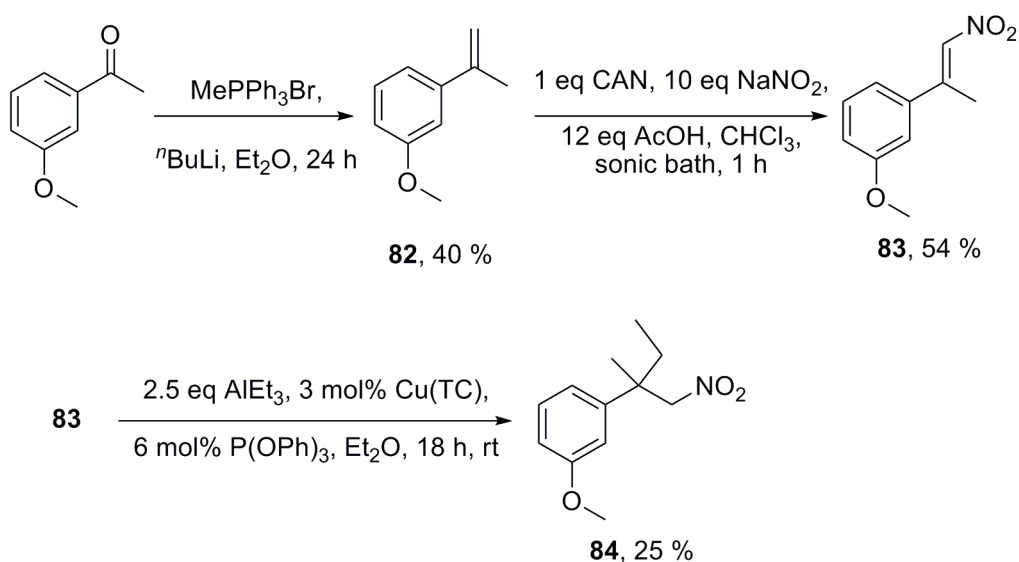
The geometry of the double bond was assigned by comparison of NMR spectroscopic data with those reported in the literature.^{37,38} Observed chemical shifts of 2.66 ppm for the methyl protons and 7.32 ppm for the alkenyl protons were in agreement with data published for (*E*)-**71**, whilst the corresponding signals for the (*Z*) isomer have been reported to be 2.20 and 7.08 ppm respectively. An alternative synthesis reported by Zagolda and Pleniewicz, using acetic anhydride and nitric acid to generate acetoxy-nitroalkane **81**, with subsequent elimination of acetic acid by NaOH was also attempted, but this did not lead to the desired product.³⁹

With nitroalkene **71** in hand, racemic conjugate additions of triethylaluminium, catalysed by $\text{Cu}(\text{OAc})_2$ or $\text{Cu}(\text{TC})$ with a range of phosphorus-based ligands were trialled (**Scheme 39**). Initial attempts at $-40\text{ }^\circ\text{C}$ in diethyl ether saw only low conversion to the desired product. Running the reactions at room temperature resulted in higher conversion, enabling purification by flash column chromatography of the combined crude products to give nitroalkane (\pm)-**72** in 18 % yield. Conditions could not be found to separate the enantiomers by gas chromatography, hence this reaction and the development of an enantioselective version could not be taken further. Differentiation between methyl and ethyl groups was anticipated to be challenging due to their similarity in size, and this is likely the reason the enantiomers could not be separated.

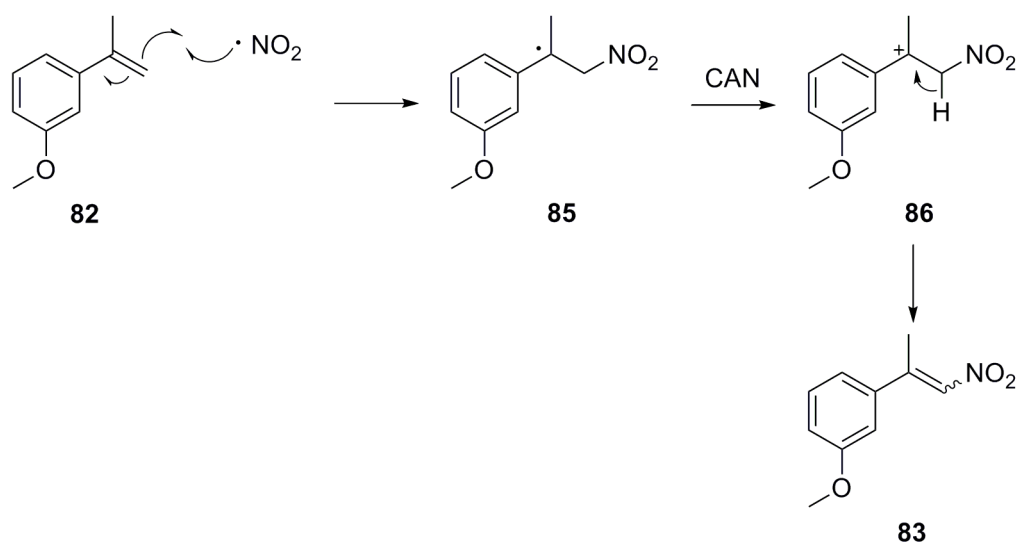


Scheme 39

With a view to finding GC-separable conjugate addition products, a different substrate, namely (*E*)-2-(3'-methoxyphenyl)-1-nitropropene **83** was synthesised (**Scheme 40**). Wittig reaction of methyltriphenylphosphonium bromide with 3-methoxyacetophenone yielded alkene **82** in 40 % yield, using a method reported by Stephens.³⁷ A CAN-catalysed nitration by sonication with sodium nitrite then afforded nitroalkene **83** in 54 % yield. This radical-based reaction proceeds by the generation of nitrite radicals by reaction of sodium nitrite with protons (**Scheme 41**).⁴⁰ The nitrite radical then attacks the C-C double bond to give nitroalkane carboradical **85**, which is oxidised to the carbocation **86** by CAN. Loss of a proton then gives the desired nitroalkene. Comparison of NMR spectroscopy data with those reported in the literature for the (*E*)-isomer gave excellent agreement, however the (*Z*) isomer has not been reported in the literature.³⁷



Scheme 40

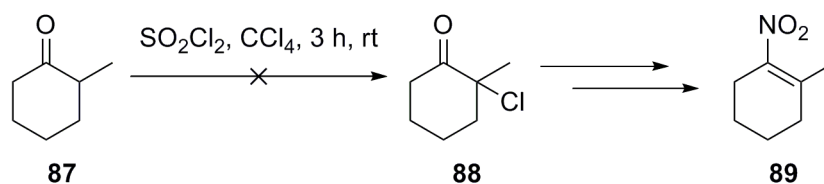


Scheme 41

Reaction of **83** with AlEt_3 (2.5 eq), Cu(TC) (3 mol%) and P(OPh)_3 (6 mol%) in Et_2O at room temperature for 18 h resulted in conjugate addition product (\pm)-**84** in 25 % yield, inseparable from 0.13 eq of starting material (**Scheme 40**). However, the enantiomers were again inseparable by gas chromatography, attributed to the similarity between the methyl and ethyl groups as above.

The synthesis of cyclic nitroalkene **89** was also attempted (**Scheme 42**), *via* chlorination of 2-methylcyclohexanone, followed by oxime formation and oxidation to the nitroalkene. Unfortunately, the first step of this synthesis,

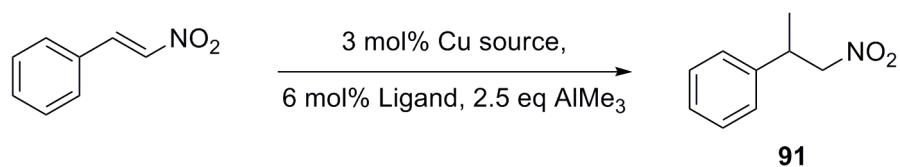
chlorination of cyclohexanone **87** by sulfuryl chloride in CCl₄, failed to give the desired product **88**.⁴¹



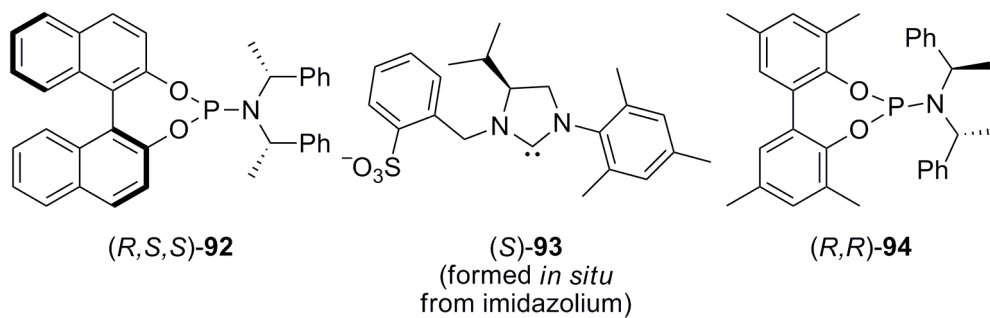
Scheme 42

Conjugate addition of a vinyl moiety was tested using (*E*)-1-decenyldiisobutylalane **90**. This was synthesised by addition of neat DIBAL-H to 1-decyne in hexane, followed by heating at 50 °C for 6 h, before direct use in reactions or storage in the freezer under argon.⁴² Reaction with (*E*)-**71** in Et₂O at −20 °C for 20 h, catalysed by Cu(TC)/P(OPh)₃, yielded only a complex mixture by NMR spectroscopy on the crude product.

With the separation of enantiomers of quaternary stereocentres proving difficult, the generation of tertiary stereocentres was instead considered. Thus, the copper-catalysed asymmetric conjugate addition of trimethylaluminium to (*E*)-nitrostyrene was studied (**Scheme 43**). The resulting nitroalkane **91** is a known compound for which GC separation conditions have been published.⁴³ Firstly, the racemic nitroalkane was successfully synthesised in 81 % yield using Cu(TC) and P(OPh)₃, stirring at −20 °C for 19.5 h then room temperature for 20.5 h (**Table 2**, entry **1**).



Chiral Ligands:



Scheme 43

Entry	Copper Salt	Ligand	Solvent	er	GC Yield (%)
1	Cu(TC)	P(OPh ₃)	Et ₂ O	50:50	81(isolated)
2	-	-	Et ₂ O	-	0
3	Cu(TC)	(<i>S,R,R</i>)- 92	Et ₂ O	68:32	8
4	Cu(OAc) ₂	(<i>S,R,R</i>)- 92	Et ₂ O	61:39	61
5	Cu(TC)	(<i>S</i>)- 93	CH ₂ Cl ₂	52:48	14
6	Cu(OAc) ₂	(<i>S</i>)- 93	CH ₂ Cl ₂	53:47	76
7	Cu(TC)	(<i>R,R</i>)- 94	Et ₂ O	28:72	50
8	Cu(OAc) ₂	(<i>R,R</i>)- 94	Et ₂ O	27:73	75
9	Cu(OAc) ₂	(<i>R,R</i>)- 94	Et ₂ O	37:63	4
10	Cu(NCMe) ₄ (BF ₄)	(<i>R,R</i>)- 94	Et ₂ O	34:66	22
11	Cu(OAc) ₂	(<i>S,S</i>)- 94	Et ₂ O	60:40	12
12	Cu(NCMe) ₄ (BF ₄)	(<i>S,S</i>)- 94	Et ₂ O	61:39	48

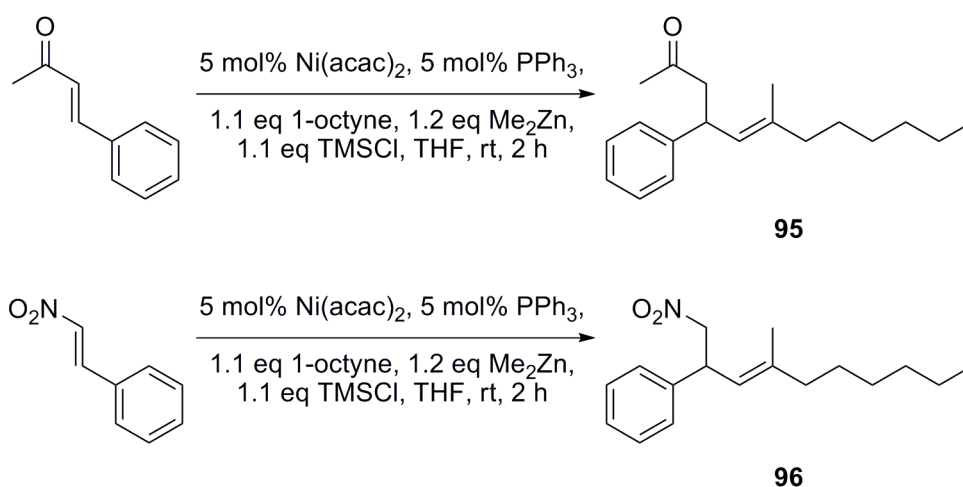
Table 2

With the racemic material in hand, calibration for yield determination by gas chromatography was achieved. Running the reaction in the absence of copper

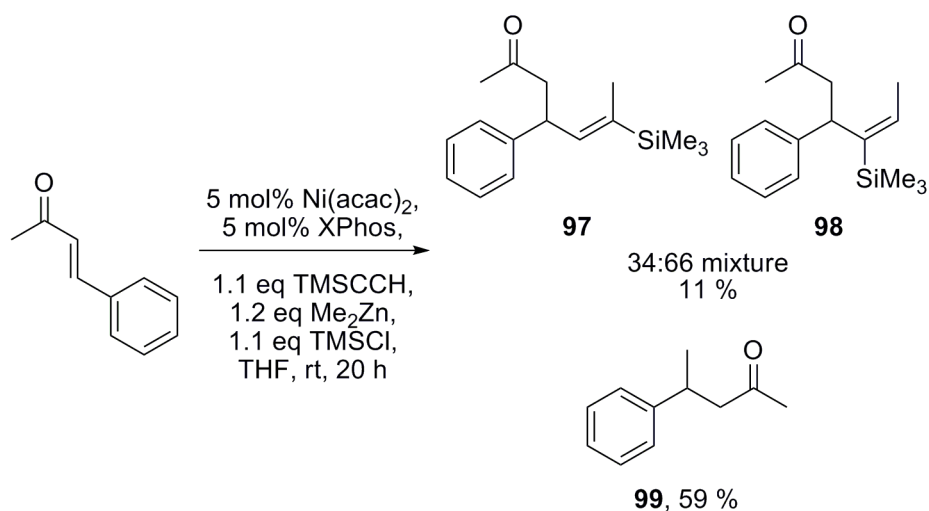
source and ligand gave no reaction, showing that the process is indeed catalysed by copper (**Table 2**, entry **2**). Of the enantioselective reactions performed at $-10\text{ }^{\circ}\text{C}$ then $0\text{ }^{\circ}\text{C}$ (**Table 2**, entries **3-8**), it can be seen that $\text{Cu}(\text{OAc})_2$ gave higher yields than $\text{Cu}(\text{TC})$ in all cases. Low to moderate enantioselectivity was achieved, with *N*-heterocyclic carbene **93** giving essentially racemic product, whilst phosphoramidite ligand **94** gave up to 46 % ee. Interestingly, use of this ligand at $-20\text{ }^{\circ}\text{C}$ for 48 h gave less enantioselectivity as well as the anticipated decrease in yield (**Table 2**, entries **9-12**).

2.1.3.2 Nickel-catalysed Tandem Coupling Reactions

Following Ikeda's report of the tandem coupling of dimethylzinc, alkyne, benzylideneacetone and trimethylsilyl chloride, the procedure's applicability to nitroalkenes was of interest (**Scheme 44**).³⁵ Initial replication of Ikeda's synthesis proved problematic, with only a trace of the desired product being present in the crude product. Optimisation of the procedure in our hands found that extending reaction time to 14 h gave an improved but still poor yield of 25 % of product **95**. Application of Ikeda's procedure to nitrostyrene failed to yield the desired product **96**. Performing the reaction in the absence of alkyne to attempt methyl conjugate addition to the nitroalkene also failed to give nitroalkane **91**.

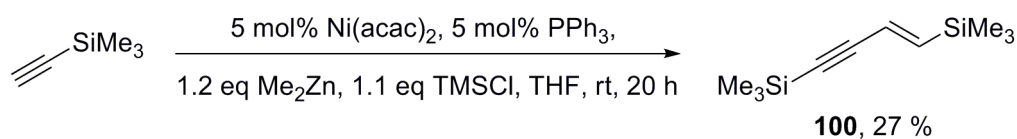


Scheme 44



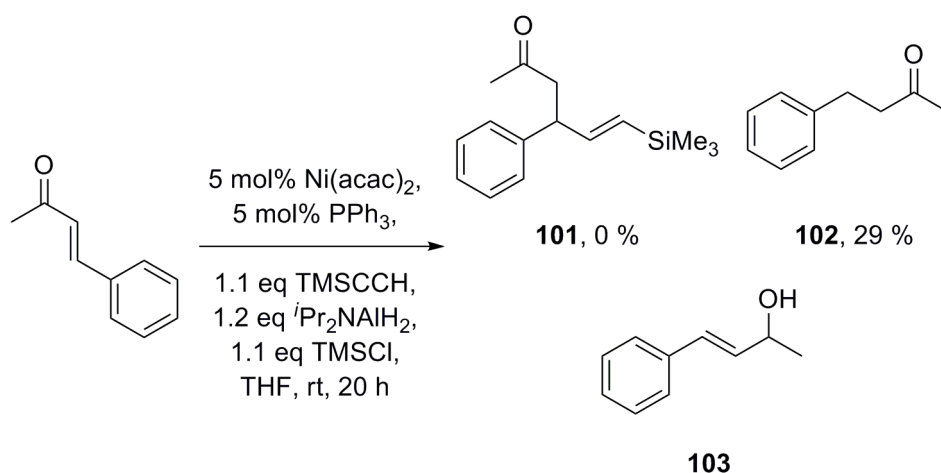
Scheme 45

Attention was then turned to tandem coupling using trimethylsilylacetylene (**Scheme 45**). Reaction of benzylideneacetone, Me₂Zn, TMS-Cl and TMS-acetylene in the presence of Ni(acac)₂ and XPhos in THF for 20 h at room temperature were found to be the best conditions tested, giving 100 % conversion, but unfortunately resulting in 4-phenylpentan-2-one **99** as the major product (59 %). The desired product **97** was produced only as the minor regioisomer in a 34:66 mixture with **98**, in 11% total yield. As a suspected by-product, the synthesis of trimethylsilylacetylene dimer **100** was investigated. Performing the reaction in the absence of benzylideneacetone with Ni(acac)₂ and triphenylphosphine yielded dimer **100** in 27 % yield (**Scheme 46**).



Scheme 46

Replacement of dimethylzinc with *i*-Pr₂NAIH₂ in a bid to generate vinylsilane **101** by introduction of H⁻ instead of Me⁻, was unsuccessful. Benzylideneacetone was instead reduced to ketone **102** (29 %) and alcohol **103** (as a mixture with impurities) (**Scheme 47**).



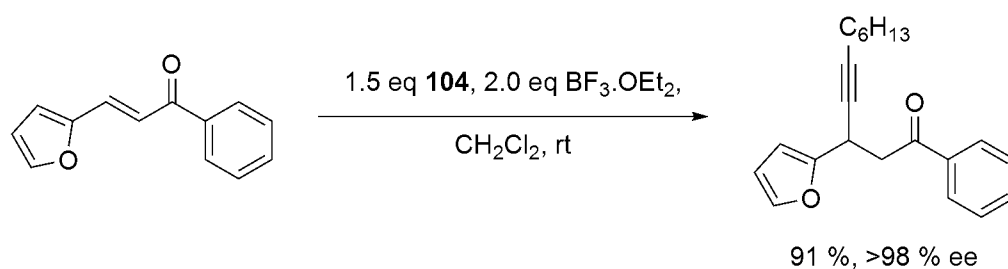
Scheme 47

2.2 Conjugate Addition to Enones

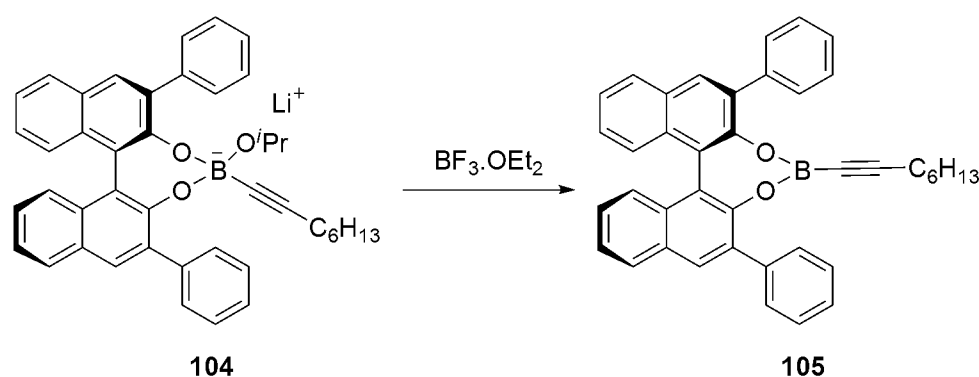
2.2.1 Introduction

Another challenging synthetic transformation is that of conjugate addition of an alkynyl group to an enone. While organocuprates are commonly employed in 1,4-addition of alkyl and alkenyl groups, π -back bonding from copper(I) to alkynes renders copper acetylides inert.^{44,45} Nevertheless, a number of methodologies successfully give 1,4-addition products in a racemic sense, and recent years have seen the development of enantioselective protocols.

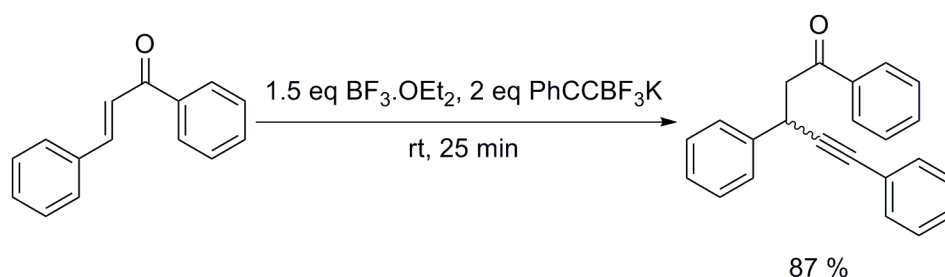
Due to the unreactivity of alkynylcopper reagents, early reports of conjugate additions of alkynes utilised alkynylboranes and alanes. Brown developed the racemic 1,4-addition of alkynyl 9-BBN reagents.⁴⁶ Enantioselective addition of alkynylboronates was first reported by Chong (**Scheme 48**).^{47,48} On treatment with $\text{BF}_3 \cdot \text{OEt}_2$, chiral diol-derived borate species **104** generates alkynylboronate **105** *in situ*, and 1,4-addition occurs with high yield and ee. Alkynylboronates are sensitive to air and moisture, and work within the Woodward group has shown that air-stable, non-hygroscopic potassium organotrifluoroborate reagents can undergo conjugate addition in a racemic fashion in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ as a Lewis acid promoter (**Scheme 49**).⁴⁹



via



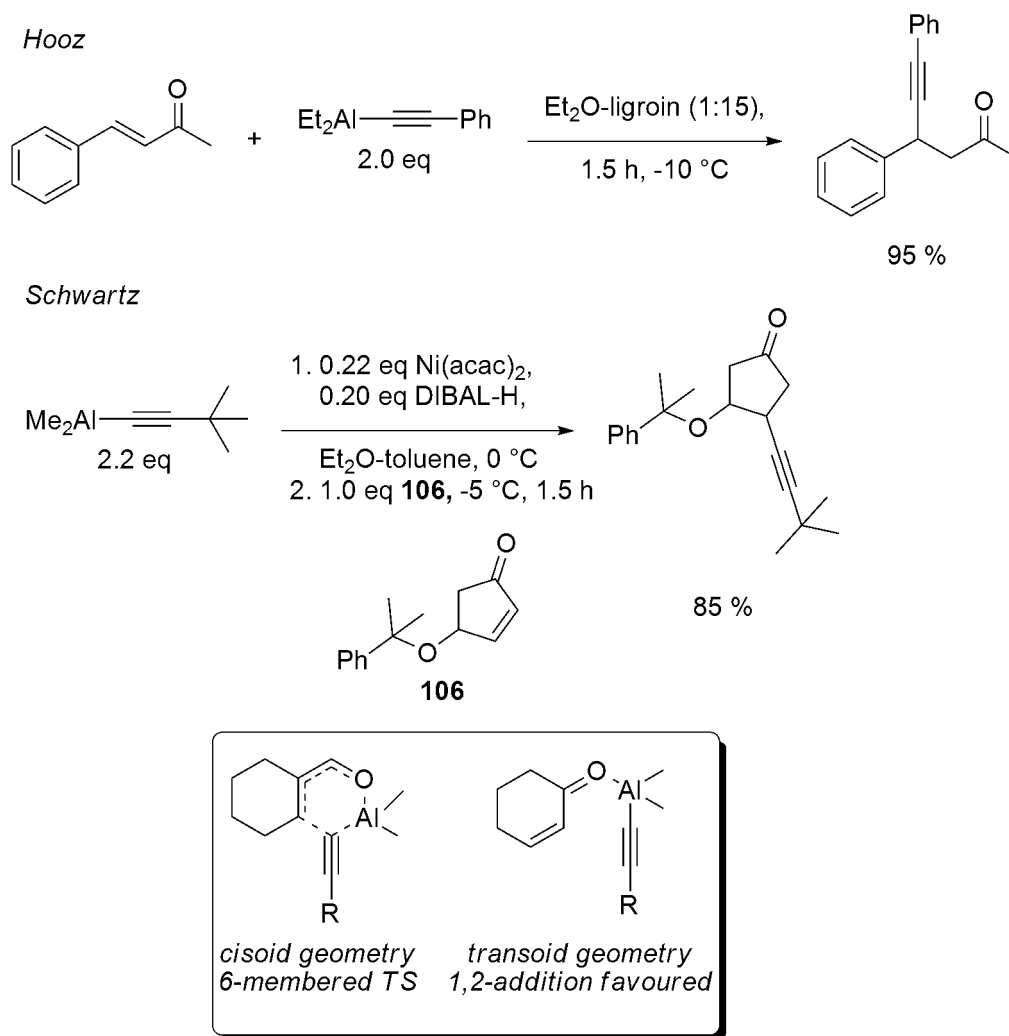
Scheme 48



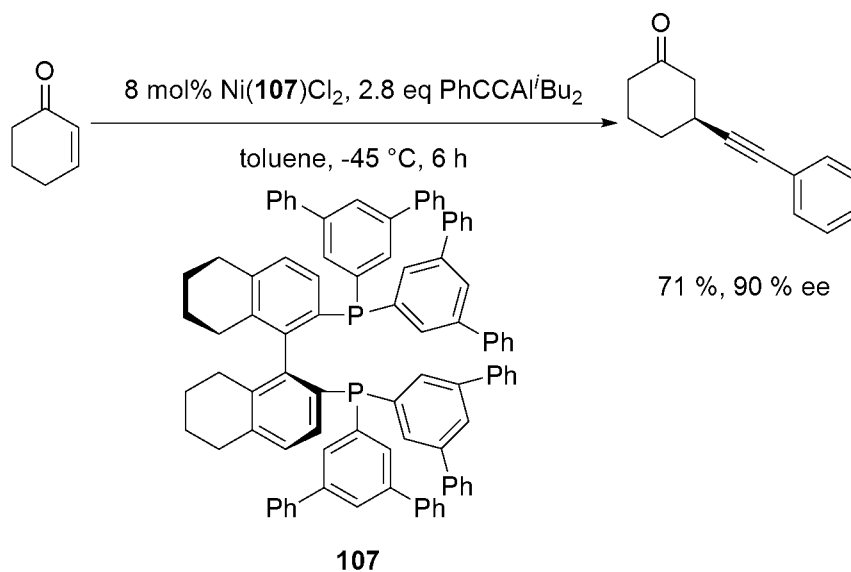
Scheme 49

Racemic 1,4-addition of alkynylaluminium reagents to acyclic enones was first reported by Hooz and Layton in 1971 (**Scheme 50**).⁵⁰ Conjugate additions to cyclic and acyclic enones present different challenges, as acyclic enones are free to adopt a cisoid geometry, allowing formation of a six-membered transition state with the incoming nucleophile adjacent to the C-C double bond. This is not possible for cyclic enones, which are locked in a transoid geometry, favouring 1,2 addition with the nucleophile adjacent to the carbonyl. However, nickel catalysis can overcome this, with a $\text{Ni}(\text{acac})_2/\text{DIBAL-H}$ -catalysed version developed by Schwartz successfully achieving 1,4-addition to cyclic enones.^{51,52} Corey and co-workers have reported the nickel-catalysed asymmetric addition of alkynylaluminiums to a cyclic enone, with good levels

of asymmetric induction. (**Scheme 51**).^{53,54} Currently there exists no reported methodology for asymmetric conjugate addition of alkynylaluminium reagents to acyclic enones.



Scheme 50

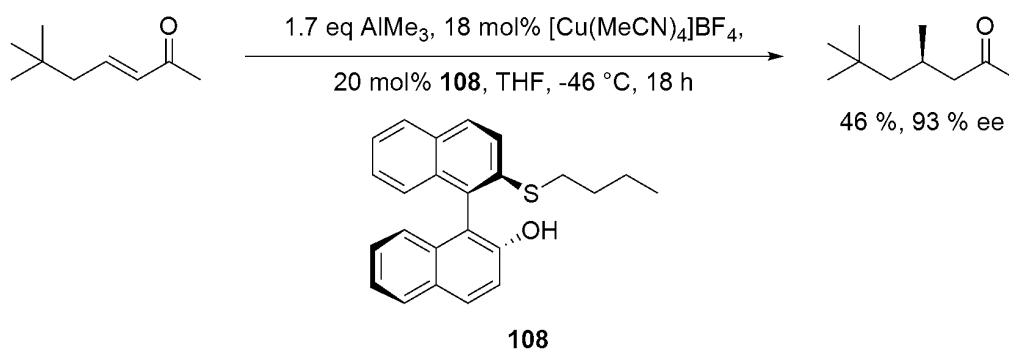


Scheme 51

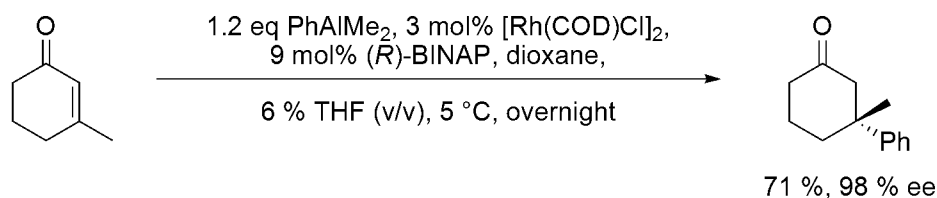
A range of other metals have also been used in alkyne conjugate addition, either as pre-formed metal-acetylide reagents or as catalysts for addition of terminal acetylenes. Rhodium-catalysed 1,4-addition of silylacetylenes has been achieved in an enantioselective manner with high ee by Nishimura and Hayashi, and the same authors have more recently reported a cobalt-catalysed variant of this procedure.^{55,56} Palladium(II) and ruthenium(II) catalysts have also been employed in additions of terminal acetylenes, although their use is limited to additions to β -unsubstituted vinyl ketones.^{57,58} Asymmetric conjugate addition of zinc alkynides mediated by a chiral aminoalcohol has been reported for both nitroalkenes and enones by Tomioka.⁵⁹

In addition to alkynylaluminium species, both alkyl- and arylaluminium reagents have previously been used successfully in asymmetric conjugate addition reactions with enones. Whilst dialkylzinc additions to cyclic enones and chalcones have been extensively studied, additions of trialkylaluminium reagents have been reported only rarely. The Woodward group have developed a $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ -catalysed procedure giving ee upto 93 % (**Scheme 52**).⁶⁰ The only previously reported addition of Me_3Al by Iwata and co-workers using a $\text{Cu}(\text{OTf})$ catalyst resulted in lower selectivity.⁶¹ Woodward and Alexakis have also reported the enantioselective conjugate addition of arylaluminium

reagents to both cyclic and acyclic enones in a rhodium-catalysed procedure (**Scheme 53**).⁶²



Scheme 52



Scheme 53

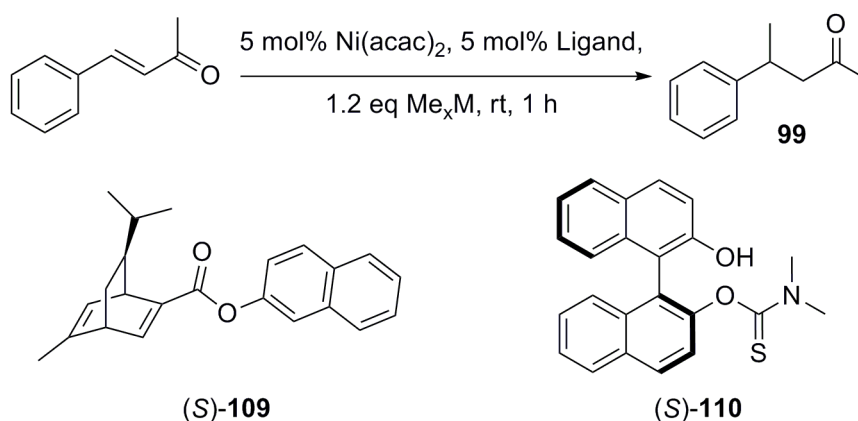
2.2.2 Aims and Objectives

The main objectives of this work were firstly to investigate the use of nickel catalysis for asymmetric conjugate addition of methyl organometallic species to enones, following the copper-catalysed trimethylaluminium addition previously developed by the Woodward group.⁶⁰ Secondly, the lack of an enantioselective method for addition of alkynylaluminium reagents to acyclic enones was also of interest. Such a method would be complementary to work by the Corey group, which has shown that alkynylaluminium reagents prepared by transmetalation from lithium can undergo asymmetric 1,4-addition to cyclic enones (**Scheme 51**).⁵⁴ Micouin has reported a preparation of alkynylaluminium species by the Lewis Base-catalysed reaction of alkynes with trimethylaluminium, and our intention was to combine this with chiral nickel-phosphine complex catalysts to yield 1,4-addition products enantioselectively.⁶³

2.2.3 Results and Discussion

2.2.3.1 Nickel-catalysed Conjugate Methyl Addition to Benzylideneacetone

As a model system, a range of chiral ligands were screened for enantioselectivity in the nickel-catalysed conjugate addition of several methyl organometallic species to benzylideneacetone. Using a standard procedure of premixing 5 mol% each of Ni(acac)₂ and a chiral ligand, followed by addition at 0 °C of 1.2 equivalents of either dimethylzinc, methylmagnesium bromide or trimethylaluminium then benzylideneacetone, and stirring at 20 °C for 1 h, a range of ligands were trialled in THF and diethyl ether (**Scheme 54**). The enantioselectivities and yields of product **99** were determined by chiral gas chromatography and are shown in **Table 3**.



Scheme 54

Entry	Organometallic	Ligand	Solvent	er	GC Yield (%)
1	Me ₂ Zn	No Ligand/Ni	THF	-	0
2	Me ₂ Zn	(<i>S,R,R</i>)- 92	THF	50:50	96
3	Me ₂ Zn	(<i>S</i>)- 109	THF	50:50	98
4	Me ₂ Zn	(<i>S</i>)- 93	THF	50:50	96
5	Me ₂ Zn	(<i>S</i>)- 110	THF	50:50	98
6	Me ₂ Zn	(<i>S,R,R</i>)- 92	Et ₂ O	50:50	34

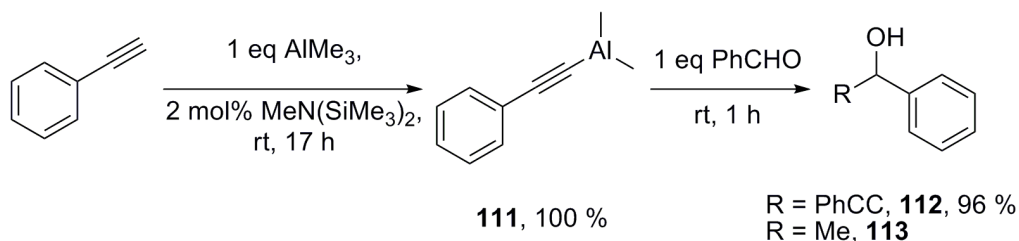
7	Me ₂ Zn	(<i>S</i>)- 109	Et ₂ O	50:50	90
8	Me ₂ Zn	(<i>S</i>)- 93	Et ₂ O	50:50	84
9	Me ₂ Zn	(<i>S</i>)- 110	Et ₂ O	51:49	36
10	MeMgBr	(<i>S,R,R</i>)- 92	THF	54:46	<2
11	MeMgBr	(<i>S</i>)- 109	THF	44:56	<2
12	MeMgBr	(<i>S</i>)- 93	THF	-	0
13	MeMgBr	(<i>S</i>)- 110	THF	49:51	<2
14	MeMgBr	(<i>S,R,R</i>)- 92	Et ₂ O	-	0
15	MeMgBr	(<i>S</i>)- 109	Et ₂ O	50:50	<2
16	MeMgBr	(<i>S</i>)- 93	Et ₂ O	56:44	<2
17	MeMgBr	(<i>S</i>)- 110	Et ₂ O	51:49	<2
18	Me ₃ Al	(<i>S,R,R</i>)- 92	THF	50:50	76
19	Me ₃ Al	(<i>S</i>)- 109	THF	50:50	80
20	Me ₃ Al	(<i>S</i>)- 93	THF	50:50	96
21	Me ₃ Al	(<i>S</i>)- 110	THF	54:46	20

Table 3

It can be seen that excellent yields were obtained using dimethylzinc in THF, irrespective of ligand (**Table 3**, entries **2-5**), and also with trimethylaluminium and imidazolium ligand **93** (**Table 3**, entry **20**). Sadly in all these cases the product was racemic. No reaction was shown to take place in the absence of the nickel-ligand complex (**Table 3**, entry **1**). Low enantioselectivity was observed on using methylmagnesium bromide, however here the yield was very low or no reaction occurred at all (**Table 3**, entries **10-17**). Thiocarbamate ligand **110** exhibited the only non-racemic products with Me₂Zn and Me₃Al (2 % and 8 % ee respectively, **Table 3**, entries **9** and **21**), albeit in fairly low yields.

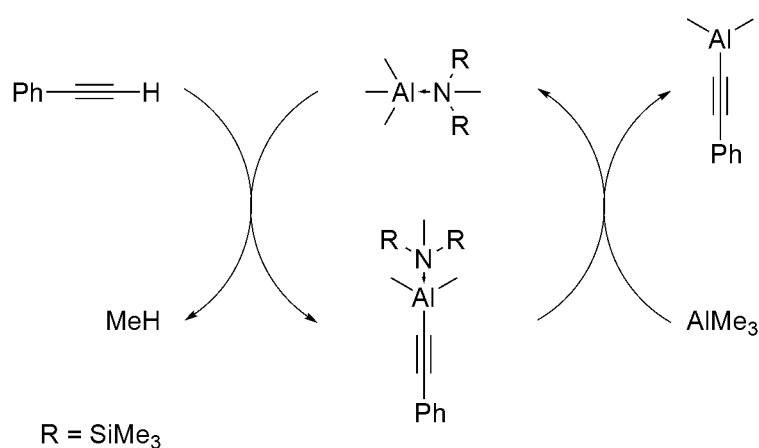
2.2.3.2 Alkynylaluminium Addition to Acyclic Enones

2.2.3.2.1 Nickel-catalysed Conjugate Addition of Alkynylaluminium to Acyclic Enones



Scheme 55

An efficient synthesis of alkynylaluminium species such as **111** has been reported by Micouin, *via* the Lewis Base-catalysed reaction of a terminal alkyne and trimethylaluminium (**Scheme 55**).⁶³ The proposed mechanism for this process involves activation of the trimethylaluminium by coordination of heptamethyldisilazane (**Scheme 56**).⁶⁴ The resulting complex metalates the alkyne, with loss of methane to give an acetylide-amine complex. Decomplexation on reaction with trimethylaluminium generates the desired alkynylaluminium species **111** and regenerates the catalytic alkylaluminium-amine complex.

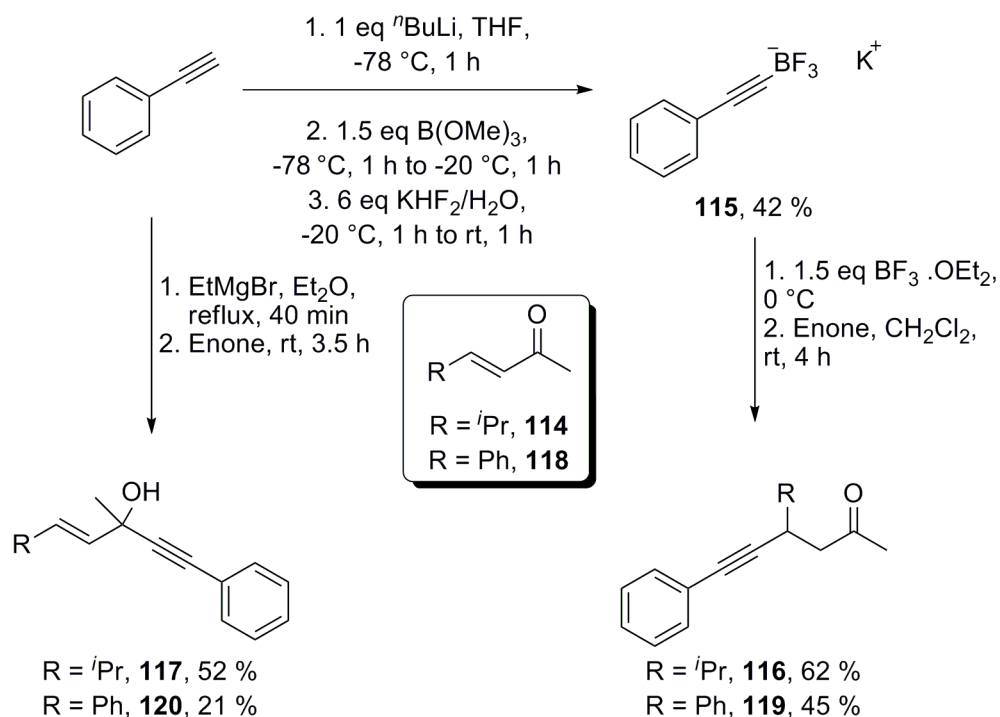


Scheme 56

In our hands, the Micouin conditions afforded a crude yield of 88 %, consisting of only a 59:41 mixture of desired product **112** and methyl addition product

113 on quenching with benzaldehyde. Optimisation by varying reaction time, temperature, and the relative amount of heptamethyldisilazane and phenylacetylene resulted in improved yield and selectivity over the methyl addition product. It was found that stirring 1.0 eq AlMe₃, 1.2 eq phenylacetylene and 6 mol% heptamethyldisilazane at either 40 °C for 5 h or 25 °C for 15.5 h gave an acceptable 87:13 mixture of product **112** and methyl addition product **113**.

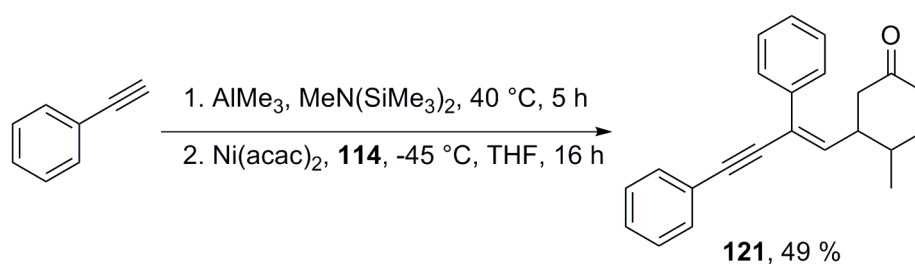
As a model system, the nickel-catalysed conjugate addition of alkynylaluminium **111** onto (*E*)-5-methylhex-3-en-2-one **114** was considered. The racemic 1,4-addition product **116** was synthesised in 62 % yield by the reaction of enone **114** with potassium (phenylethynyl)trifluoroborate **115** and BF₃.OEt₂ (**Scheme 57**). The trifluoroborate was generated from phenylacetylene by treatment with ⁿBuLi, trimethylborate and potassium hydrogen fluoride in a moderate yield of 42 %. Racemic 1,2-addition product **117** was also synthesised. Grignard reaction of phenylacetylene and ethylmagnesium bromide at 40 °C for 4 h followed by addition to enone **114** at room temperature afforded enol **117** in 52 % yield. Similarly, racemic 1,4- and 1,2-addition products **119** and **120** were synthesised from benzylideneacetone **118** in 45 and 21 % yield respectively.



Scheme 57

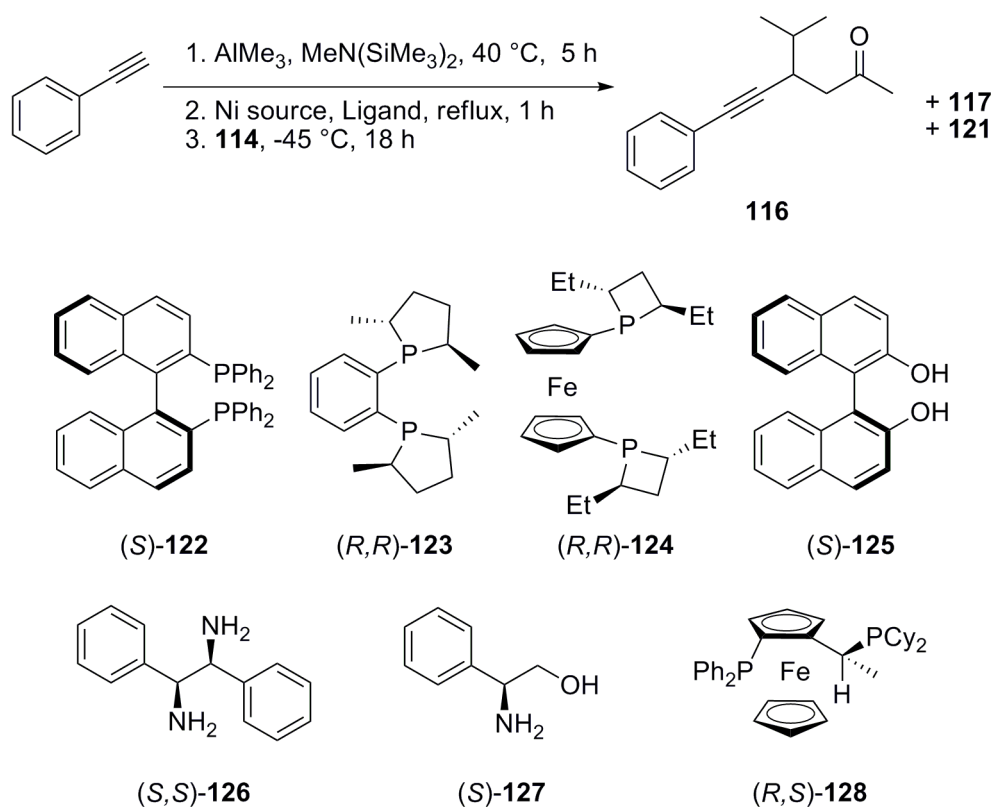
Initial attempts at nickel-catalysed asymmetric addition in toluene found background uncatalysed reaction readily occurred. To combat this, a range of solvents were screened in the absence of nickel for 4 h at $-45\text{ }^{\circ}\text{C}$. It was found that the most suitable solvents were THF and 2-MeTHF, in which no background reaction occurred at all. In diethyl ether, acetonitrile and 1,2-DME, a small amount of background reaction was observed, while toluene and dichloromethane facilitated significant uncatalysed reaction. The ethereal solvents can form a complex with the organoaluminium species through coordination of the oxygen lone pair (as can acetonitrile through its nitrogen lone pair), inhibiting uncatalysed reaction with the enone. In contrast, the enone is free to coordinate to the aluminium reagent in toluene and dichloromethane, allow uncatalysed reaction to occur more readily.

On using nickel salts in the absence of a chiral ligand, the formation of enyne **121** was observed. Reaction catalysed by 9 mol% $\text{Ni}(\text{acac})_2$ in THF generated the enyne in 49 % yield (**Scheme 58**). This is presumed to occur by initial 1,4-addition followed by carboalumination of the alkynyl group by a second molecule of alkynylaluminium **111**.



Scheme 58

A range of nickel salts and chiral ligands were then screened for enantioselectivity, regioselectivity of 1,4-addition and chemoselectivity over formation of enyne **121**. The nickel salt and chiral ligand (9 mol% each) were heated at reflux for 1 h before cooling to $-45\text{ }^\circ\text{C}$ and addition of alkynylaluminium **111**. Enone **114** was added and reaction was carried out at $-45\text{ }^\circ\text{C}$ for 18 h (**Scheme 59**). After quenching with HCl, the reaction mixture was analysed by chiral GC and NMR to give the results in **Table 4**.



Scheme 59

Entry	Ni source	Ligand	Solvent	Conversion (%) ^a	Yield 1,2 (%) ^b	Yield 1,4 (%) ^b	er 1,4 ^b	Yield Enyne (%) ^c
1	NiCl ₂ .6H ₂ O	(S)- 122	THF	95	1	9	50:50	25
2	NiCl ₂ .6H ₂ O	(R,R)- 123	THF	80	1	7	50:50	44
3	NiCl ₂ .6H ₂ O	(S)- 110	THF	95	1	15	50:50	56
4	Ni(acac) ₂	(S)- 122	THF	46	2	5	49:51	23
5	Ni(acac) ₂	(R,R)- 123	THF	91	1	10	50:50	27
6	Ni(acac) ₂	(R,R)- 124	THF	95	1	11	49:51	55
7	Ni(acac) ₂	(S)- 110	THF	98	1	14	47:53	47
8	NiCl ₂	(S)- 122	THF	60	3	8	49:51	19
9	NiCl ₂	(R,R)- 123	THF	37	2	4	49:51	9
10	NiCl ₂ .6H ₂ O	(S)- 122	1,2-DME	88	6	17	52:48	N.D.
11	NiCl ₂ .6H ₂ O	(R,R)- 123	1,2-DME	90	5	33	50:50	N.D.
12	NiCl ₂ .6H ₂ O	(R,R)- 124	1,2-DME	91	5	29	50:50	N.D.
13	NiCl ₂ .6H ₂ O	(S)- 110	1,2-DME	92	6	31	48:52	N.D.
14	Ni(acac) ₂	(R,R)- 123	1,2-DME	91	4	26	50:50	N.D.
15	Ni(acac) ₂	(R,R)- 124	1,2-DME	92	4	28	50:50	N.D.
16	Ni(acac) ₂	(S)- 110	1,2-DME	92	4	31	47:53	N.D.
17	NiCl ₂	(S)- 122	1,2-DME	82	10	29	49:51	N.D.
18	NiCl ₂	(R,R)- 123	1,2-DME	81	8	26	50:50	N.D.
19	NiCl ₂	(R,R)- 124	1,2-DME	82	5	31	50:50	N.D.
20	NiCl ₂ .6H ₂ O	(S)- 125	THF	79	0	9	50:50	62
21	NiCl ₂ .6H ₂ O	(S,S)- 126	THF	75	0	9	51:49	44
22	NiCl ₂ .6H ₂ O	(S)- 127	THF	86	0	10	50:50	67
23	Ni(acac) ₂	(S,S)- 126	THF	41	2	5	49:51	23
24	-	-	1,2-DME	43	2	5	49:51	N.D.
25	-	-	THF	28	1	1	48:52	1

^a Based on depletion of starting material as determined by GC.

^b Determined by GC.

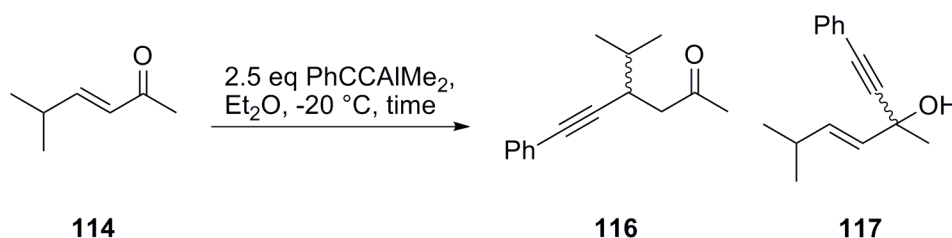
^c Determined by ¹H NMR spectroscopy.

Table 4

The results in **Table 4** show that while high conversion occurred in the

It can be seen from **Table 5** that in all cases good conversion was achieved, and little or no enyne **121** was generated. Using nickel as the catalyst (**Table 5**, entry **4**), the yield of conjugate addition product **116** was improved over the reactions in **Table 4**. Use of CuBr gave the highest yield of 1,4-addition product (44 %) and was also most selective for 1,4- over 1,2-addition (**Table 5**, entry **1**). Sadly all these reactions gave racemic product. Copper-catalysed processes involving alkynes generally result in coordination of the alkyne to copper, so this was an interesting result.⁶⁵

Given the lack of enantioselectivity seen in these reactions, it was attempted to optimise the racemic reaction. In order to ascertain the optimum reaction time for alkynylaluminium addition, the uncatalysed reaction of enone **114** with Me₂AlCCPh was carried out at -20 °C in Et₂O, varying the reaction time (**Scheme 61**). Monitoring the reactions by GC gave the results in **Table 6**. Optimal reaction time was 2.5 h, giving 50 % 1,4-addition product with nearly complete conversion, however, in all cases competing side-reactions were observed.



Scheme 61

Time	Conversion (%) ^a	Yield 1,4 (%) ^b	Yield 1,2 (%) ^b
10 min	81	33	16
30 min	89	40	15
1 h	92	35	19
1.5 h	92	45	17
2 h	94	47	20
2.5 h	94	50	19
3 h	96	44	20

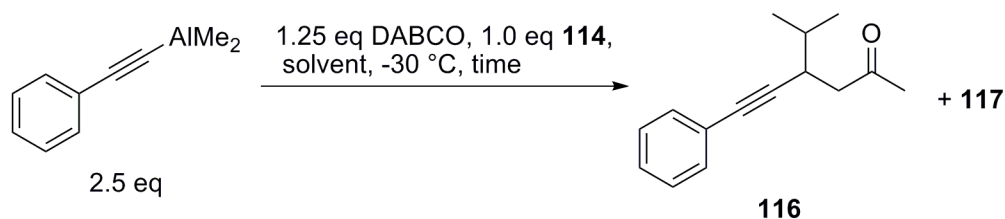
3.5 h	96	27	21
4 h	98	45	22
4.5 h	98	48	21
5 h	98	39	22
5.5 h	99	48	20

^a Based on depletion of starting material as determined by GC.

^b Determined by GC.

Table 6

The effect of adding DABCO to moderate the reactivity of the organoaluminium species was also investigated (**Scheme 62**). The addition of half an equivalent of DABCO with respect to the alkynylaluminium was used as an *in situ* equivalent of using DABAL-Me₃ methodology developed by the Woodward group for methyl additions.⁶⁶ It can be seen from **Table 7** that in a variety of solvents conversion and yield were both dramatically curtailed in the presence of DABCO.



Scheme 62

Solvent	DABCO	Time	Conversion (%) ^a	Yield 1,4 (%) ^b	Yield 1,2 (%) ^b
THF	N	10 min	14	0	0
THF	Y	10 min	20	0	0
THF	N	2 h	40	0	0
THF	Y	2 h	22	0	0
CH ₂ Cl ₂	N	1 h	58	18	10
CH ₂ Cl ₂	Y	1 h	22	0	0
MTBE	N	1 h	81	36	16
MTBE	Y	1 h	28	0	0

Toluene	N	1 h	80	42	16
Toluene	Y	1 h	17	0	0
Et ₂ O	Y	1 h	24	0	0
Et ₂ O	Y	2 h	26	0	0

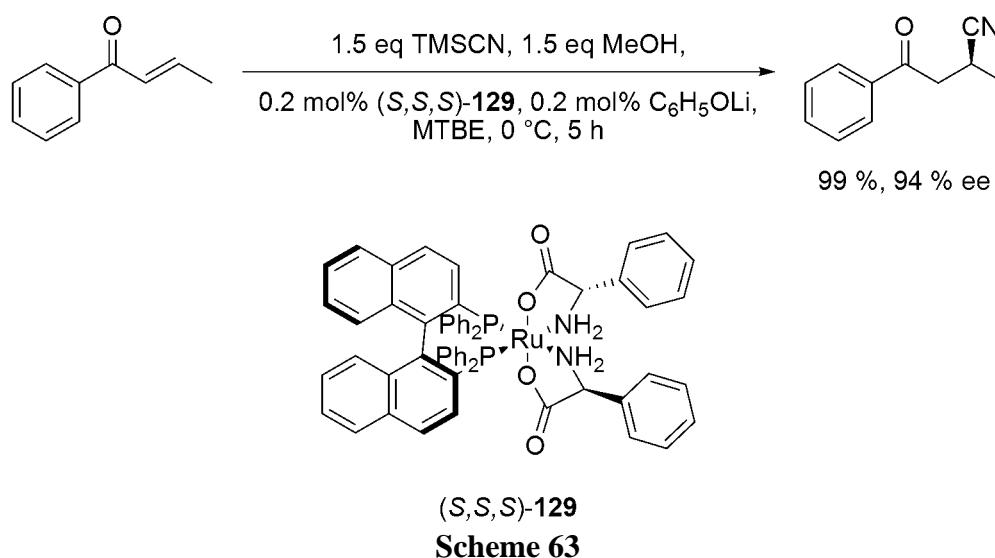
^a Based on depletion of starting material as determined by GC.

^b Determined by GC.

Table 7

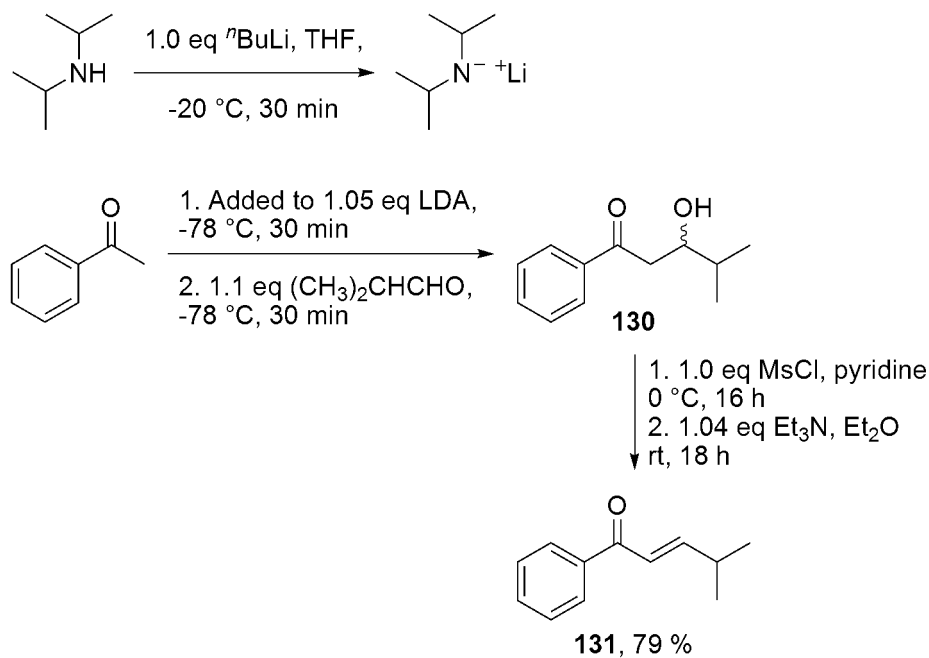
2.2.3.2.2 Application of Ruthenium-catalysed Hydrocyanation Conditions to Alkynylaluminium Conjugate Addition

Enantioselective 1,4-addition of cyanide to enones using ruthenium catalyst **129** was reported by Ohkuma (**Scheme 63**).⁶⁷ The resulting β -cyano ketones were obtained in excellent yield and ee using MTBE as the solvent. The cyanide was generated *in situ* from TMSCN and an equimolar amount of MeOH. This system appeared potentially useful for application to the conjugate addition of alkynylmetal species.



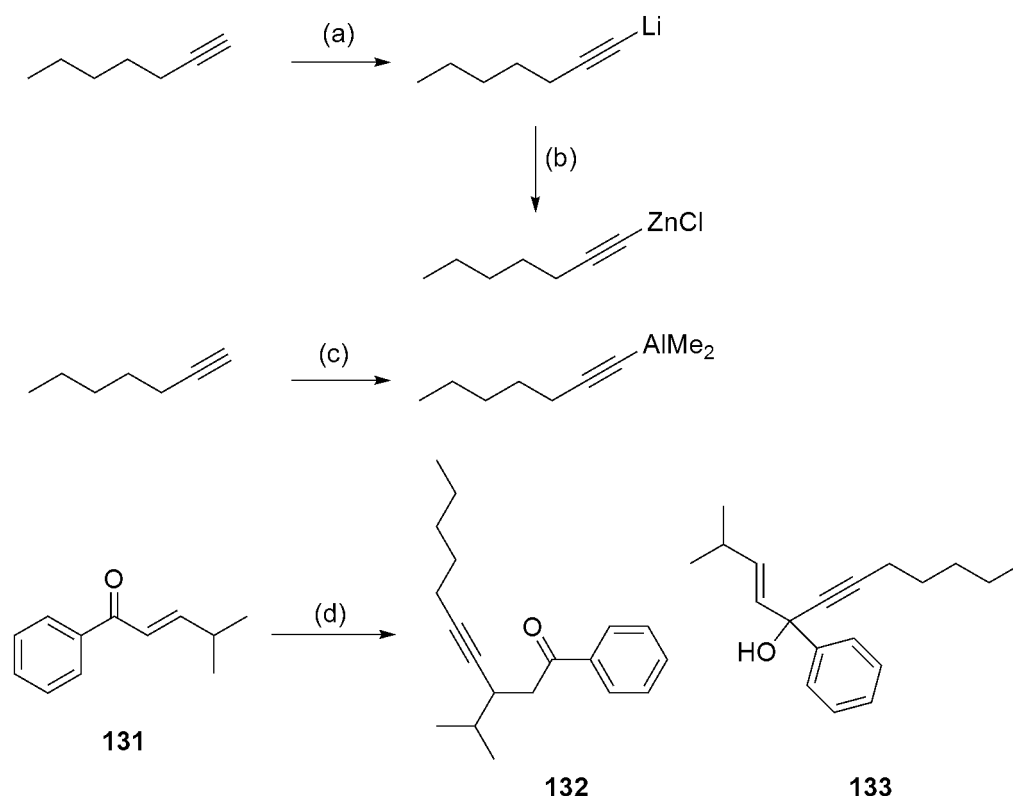
Given that addition of cyanide worked best for enones substituted with a phenyl at the carbonyl and an alkyl on the alkene, enone **131** was selected as a substrate for our investigations, and was synthesised *via* an aldol condensation (**Scheme 64**).⁴⁷ Initially acetophenone was treated with LDA and then reacted

with isobutyraldehyde. Mesylation and subsequent elimination of the alcohol **130** resulted in 60 % overall yield of the enone. This increased to 79 % when purified by distillation instead of column chromatography.



Scheme 64

The ruthenium catalyst was synthesised according to Ohkuma's previous report.⁶⁸ Sodium (*S*)-phenylglycinate was prepared using a procedure reported by Shionoya, and reacted with a mixture of $[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$ and (*S*)-BINAP in DMF to give catalyst **129** in 74 % yield.⁶⁹



Conditions:

a: $n\text{BuLi}$, THF, $-70\text{ }^\circ\text{C}$, 10 min

b: ZnCl_2 , THF, $-70\text{ }^\circ\text{C}$ to rt, 20 min

c: AlMe_3 , $\text{MeN}(\text{SiMe}_3)_2$, $25\text{ }^\circ\text{C}$, 16 h

d: 2 mol% (S,S,S)-**129**, 1.5 eq (1-heptynyl)M, MTBE, $0\text{ }^\circ\text{C}$, 3 h

M = Li, 32 % **133**

M = ZnCl, no reaction

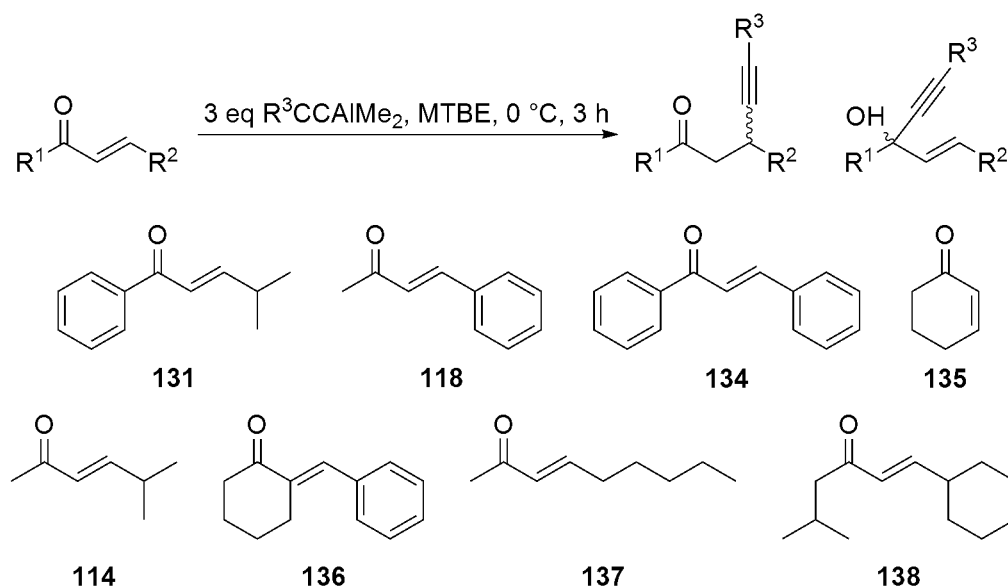
M = AlMe_2 , 37 % **132**

Scheme 65

Ohkuma's procedure was modified to use different alkynyl metal species, in order to investigate their reactivity (**Scheme 65**). Using 2 mol% catalyst loading, 1-heptynyllithium added to enone **131** in a 1,2-manner to give **133** in 32 % yield. The organolithium reagent was also treated with a stoichiometric amount of zinc chloride to give 1-heptynylzinc chloride, but this failed to react with the enone. Use of dimethyl(1-heptynyl)aluminum however, afforded the desired 1,4-addition product **132** in 37 % yield. Reducing the catalyst loading to 1 mol% saw the yield drop to 26 %.

In an effort to increase the yield of 1,4-addition product, it was found that increasing the amount of alkynylaluminium reagent to three equivalents, without the catalyst present, gave good yields of racemic products

(**Scheme 66**). Thus, a range of enone substrates gave ynones and propargylic alcohols in fair to excellent overall yields on addition of dimethyl(1-heptynyl)aluminium (**Table 8**, entries **1-8**). The process worked equally well with an aromatic alkyne (**Table 8**, entries **9** and **10**).



Scheme 66

Entry	Enone	R^3	Yield 1,4 (%) ^a	Yield 1,2 (%) ^a
1	131	C_5H_{11}	98	0
2	118	C_5H_{11}	25	38
3	134	C_5H_{11}	71	0
4	135	C_5H_{11}	0	67
5	114	C_5H_{11}	29	31
6	136	C_5H_{11}	7	68
7	137	C_5H_{11}	30	33
8	138	C_5H_{11}	23	0
9	131	Ph	100	0
10	134	Ph	38	0

^a Isolated yield.

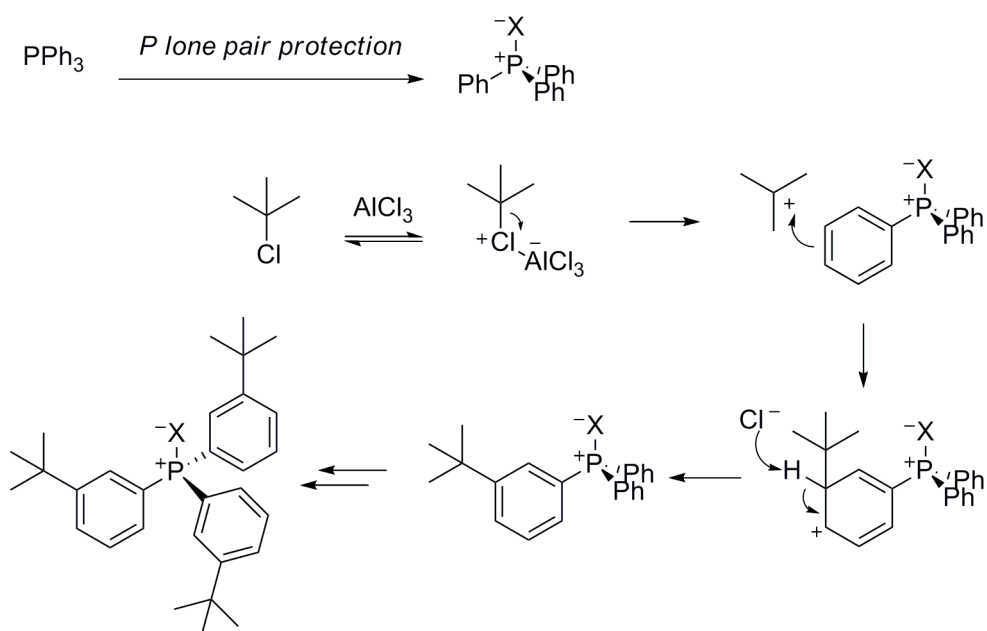
Table 8

The regioselectivity of the reaction depends on the nature of the enone; substrates bearing a phenyl ring at the carbonyl give exclusively 1,4 addition,

whilst those with phenyl substitution solely on the alkene favour 1,2-addition. Aliphatic substitution at both ends of the enone leads to a roughly 1:1 mixture of 1,4- and 1,2-addition. Cyclohexenone gave solely 1,2-addition.

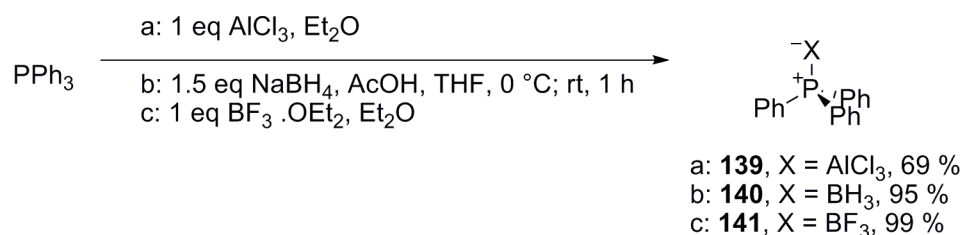
2.2.3.2.3 Friedel-Crafts Alkylation of Arylphosphines

The ligand **107** used by Corey in conjugate alkynyl additions to cyclic enones is a sterically bulky bisphosphine ligand synthesised in several steps (**Scheme 51**).⁵⁴ With a view to the quick incorporation of sterically demanding groups onto arylphosphine aromatic rings, Friedel-Crafts alkylation of triphenylphosphine derivatives was attempted (**Scheme 67**).



Scheme 67

Initially, protection of the phosphorus lone pair was achieved by synthesis of aluminium chloride, borane and boron trifluoride complexes **139-141** (**Scheme 68**). Reaction of Ph_3P with AlCl_3 furnished complex **139** in 69 % yield, while reaction with $\text{BF}_3 \cdot \text{OEt}_2$ gave complex **141** in 99 % yield. Treatment of the phosphine with NaBH_4 then acetic acid afforded borane adduct **140** in 95 %.

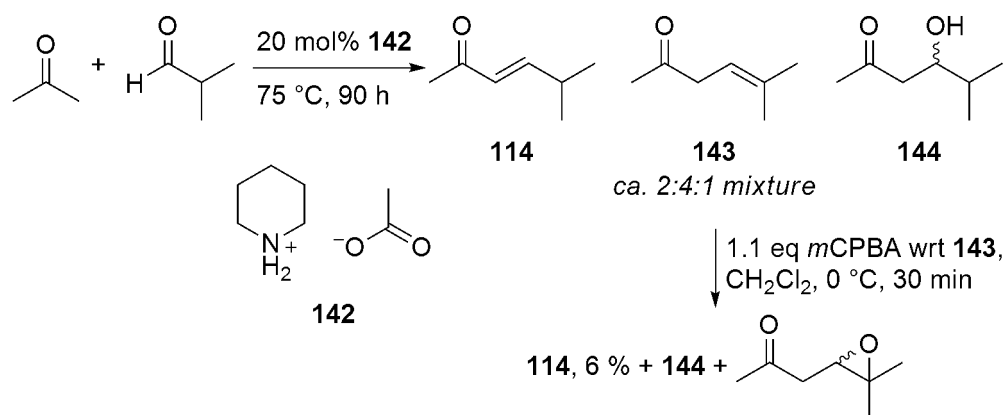


Scheme 68

Unfortunately, Friedel-Crafts reactions on complexes **139** and **140** were unsuccessful. Reactions with AlCl₃ and ^tBuCl in hexane at reflux or room temperature led to exchange of the borane adduct for AlCl₃, or formation of a mixture of Ph₃P and Ph₃P=O. Use of ^tBuOH and H₃PO₄ resulted in either no reaction or Ph₃P formation.

2.2.3.2.4 Organocatalytic Preparation of (*E*)-5-methylhex-3-en-2-one

(*E*)-5-Methylhex-3-en-2-one **114** was generally obtained from commercial sources, however, it was also synthesised using an organocatalytic method reported by List.⁷⁰ Piperidinium acetate **142** was prepared and used to catalyse the aldol condensation reaction of acetone and isobutyraldehyde. The published procedure was modified to use sealed microwave vials in an oil bath to allow larger scale reaction, which afforded a 2:4:1 mixture of the desired enone, its isomer **143** and aldol product **144** which had not undergone elimination (**Scheme 69**). Treatment with *m*CPBA allowed oxidation of isomer **143** which could then be removed by column chromatography. A low overall yield of 6 % was achieved; however, this furnished 347 mg for use in subsequent reactions.

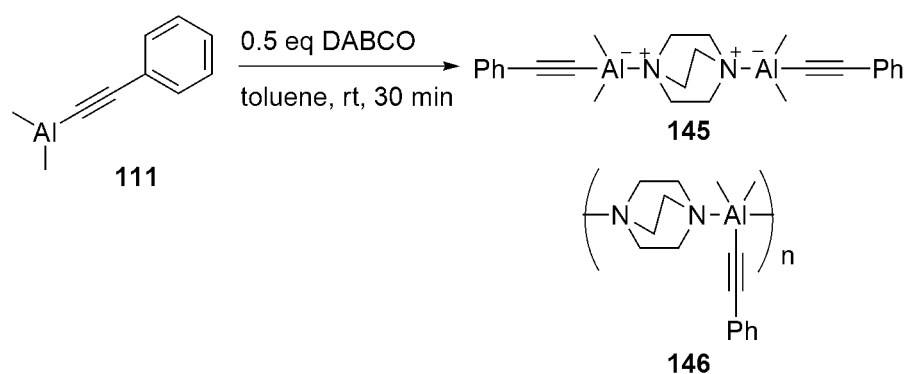


Scheme 69

2.2.3.3 Alkynyl DABAL-Me₃ Analogues

As DABAL-Me₃ is a useful, air-stable analogue of trimethylaluminium, a similar variant of dimethyl(alkynyl)aluminium compounds would be attractive. This would be a more practical and safer alternative to preparation of the alkynylaluminium and subsequent *in situ* addition of DABCO described above.

Initially, dimethyl(phenylethynyl)aluminium **111** was synthesised and a solution of 0.5 equivalents of DABCO in toluene was added at room temperature. After stirring for 30 min, the solvent was evaporated to give a white solid. While this exhibited stability in air for several minutes, NMR spectroscopy in C₆D₆ showed the presence of two new species, consistent with desired product **145** and 1:1 polymeric structure **146** (**Scheme 70**). The DABCO CH₂ singlet at 2.47 ppm had been replaced by two new signals at 2.27 and 2.11 ppm in a 3.6:1 ratio. In order to rectify this, and obtain solely the desired product as crystalline material for X-ray diffraction, variations in solvent, concentration and recrystallisation were made, and phenylacetylene was also replaced with its 4-*tert*-butyl substituted derivative. None of these furnished suitable crystals for analysis.

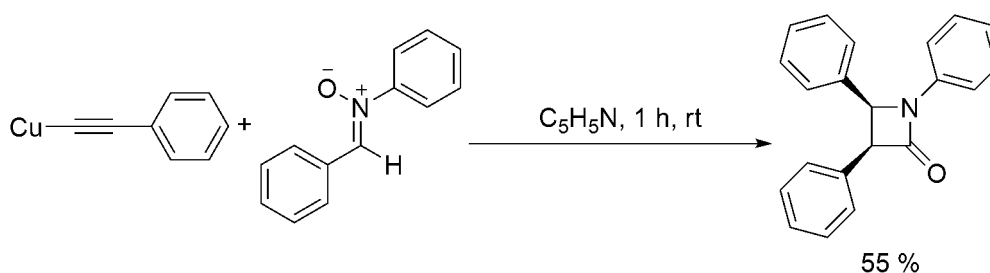


Scheme 70

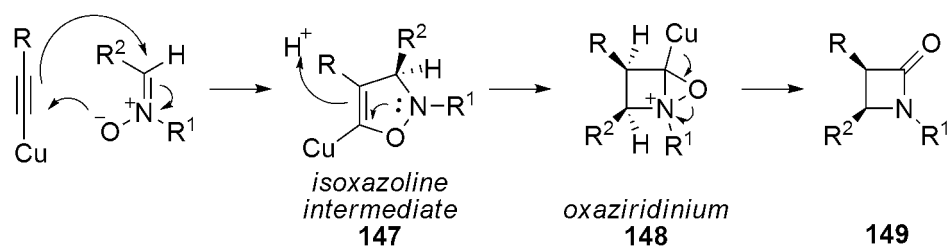
An alternative approach was tried by reacting DABAL-Me₃ with phenylacetylene. DABAL-Me₃ was prepared in 95 % yield from neat trimethylaluminium and 0.5 equivalents of DABCO in toluene.⁶⁶ However, on reaction with two equivalents of phenylacetylene in toluene, this also led to granules of insufficient size for X-ray analysis.

2.2.3.4 Use of Organoaluminium Reagents in the Kinugasa Reaction

The Kinugasa reaction between copper(I) phenylacetylide and a nitron was first reported in 1972.⁷¹ Moderate yields of *cis*-β-lactams were obtained after 1 h at room temperature in dry pyridine (**Scheme 71**). The generally accepted mechanism for this reaction proceeds through a [3+2] cycloaddition between the copper acetylide and nitron to give an isoxazoline intermediate **147** (**Scheme 72**). Attack of the C-C double bond by the nitrogen lone pair and protonation lead to oxaziridinium species **148**, which rearranges to β-lactam **149**. The stereospecificity of the reaction is postulated to be due to protonation from the least hindered side.⁷²



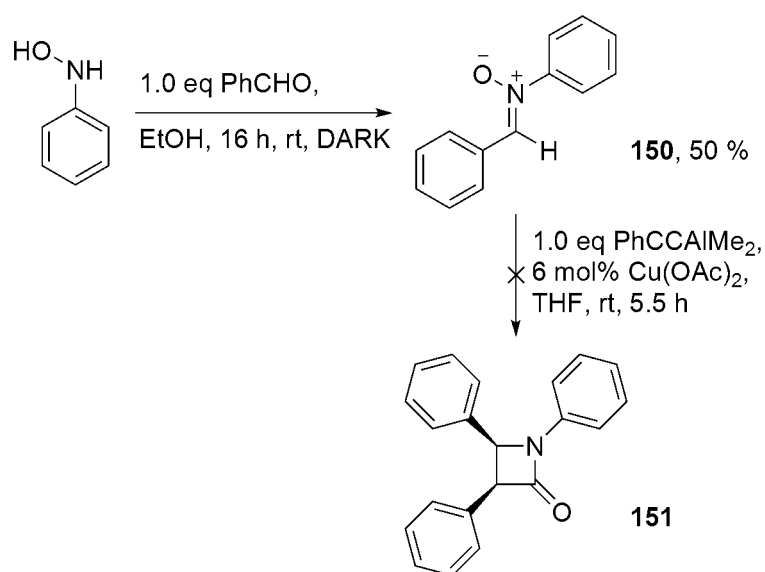
Scheme 71



Scheme 72

Since these early reports, this procedure has received little attention in the literature. Several groups have published enantioselective variants of the reaction using a copper source in conjunction with a chiral catalyst.⁷³⁻⁷⁷ We hoped to utilise the dimethylalkynylaluminium reagents as an alternative to this approach. A related procedure involving cyclisation of alkynylaluminium species with oximes has been reported by Micouin.⁷⁸

N-Phenylhydroxylamine was purified to remove sodium chloride impurities prior to reaction with benzaldehyde in EtOH in the dark to give nitron **150** in 50 % overall yield.⁷⁹ Dimethyl(phenylethynyl)aluminium **111** was prepared and added to a solution of nitron **150** in THF at room temperature. The reaction was run for 5.5 h both in the absence and presence of Cu(OAc)₂ (6 mol%), however, in both cases no desired β -lactam **151** was detected by NMR spectroscopy (**Scheme 73**).



Scheme 73

2.3 Conclusions

A move to the development of asymmetric conjugate addition reactions also met with mixed fortunes. Additions to nitroalkenes resulted in products that could not be separated by chiral gas chromatography, meaning that enantioselectivity could not be measured and hence optimised. Simple conjugate additions of methyl organometallics to nitrostyrene and benzylideneacetone saw only low to modest asymmetric induction in the systems screened.

Conjugate addition of alkynylaluminium to (*E*)-5-methylhex-3-en-2-one has been plagued by issues which required optimisation, including formation of the alkynylaluminium reagent itself. With this rectified, it was found that high levels of background reaction occurred in toluene, and that ethereal solvents and acetonitrile prevent this, especially THF. With all transition metal and ligand conditions screened, essentially racemic products were formed, and in many cases, nickel-catalysed reactions resulted in a large amount of undesired carboalumination of the initially formed 1,4-addition product.

The racemic 1,4-addition of alkynylaluminium to acyclic enones was achieved in good to excellent yields employing MTBE as the solvent with three equivalents of alkynylaluminium, although regioselectivity remains an issue depending on the enone substrate.

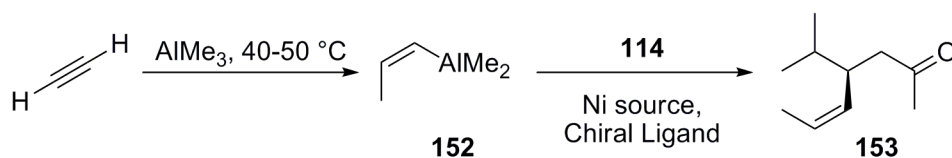
2.4 Future Studies

Much of the work carried out has not been successful; however, there are several positive results that could be built upon in the future.

The successful conjugate addition of an alkynylaluminium to an enone catalysed by CuBr-Josiphos was a surprising result, and although only a moderate yield of 44 % was achieved in our initial experiment, further work will hopefully improve on this. With the preparation of the racemic

1,4-addition products in MTBE optimised, it is also envisaged that further catalyst screening could lead to an enantioselective variant.

The carboalumination reaction of trimethylaluminium with acetylene to yield vinylaluminium reagent **152** is currently unexploited chemistry (**Scheme 74**), recently reported by McGuinness.⁸⁰ If successful, this could be utilised in conjugate addition chemistry to easily access chiral vinyl-substituted moieties such as **153**. Furthermore, an alternative way to generate vinylaluminium species will be discussed in Chapter 4, and the use of these in conjugate addition will be studied within the Woodward group.



Scheme 74

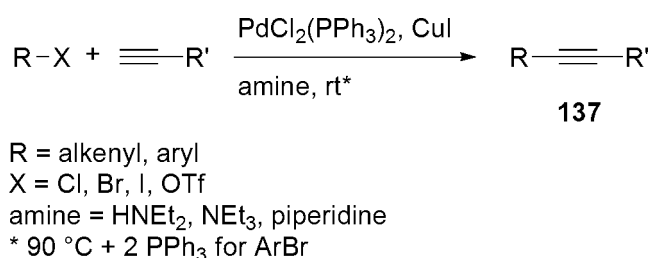
Another potential avenue for the introduction of alkynyl substituents into α,β -unsaturated compounds would be the rhodium-catalysed asymmetric conjugate addition of potassium alkynyltrifluoroborates. Related transformations of aryl and alkenyltrifluoroborates have been reported by Darses and Genêt.^{81,82} Chong has reported asymmetric 1,4-addition of alkynylboronates to enones with over 98 % ee, although these reagents have been reported to be sensitive to air and moisture, and a procedure using the more easily-handled, air-stable trifluoroborates has not yet been reported.^{47,48,83}

CHAPTER 3

Pd-catalysed Cross-Coupling of Alkynylaluminium Reagents

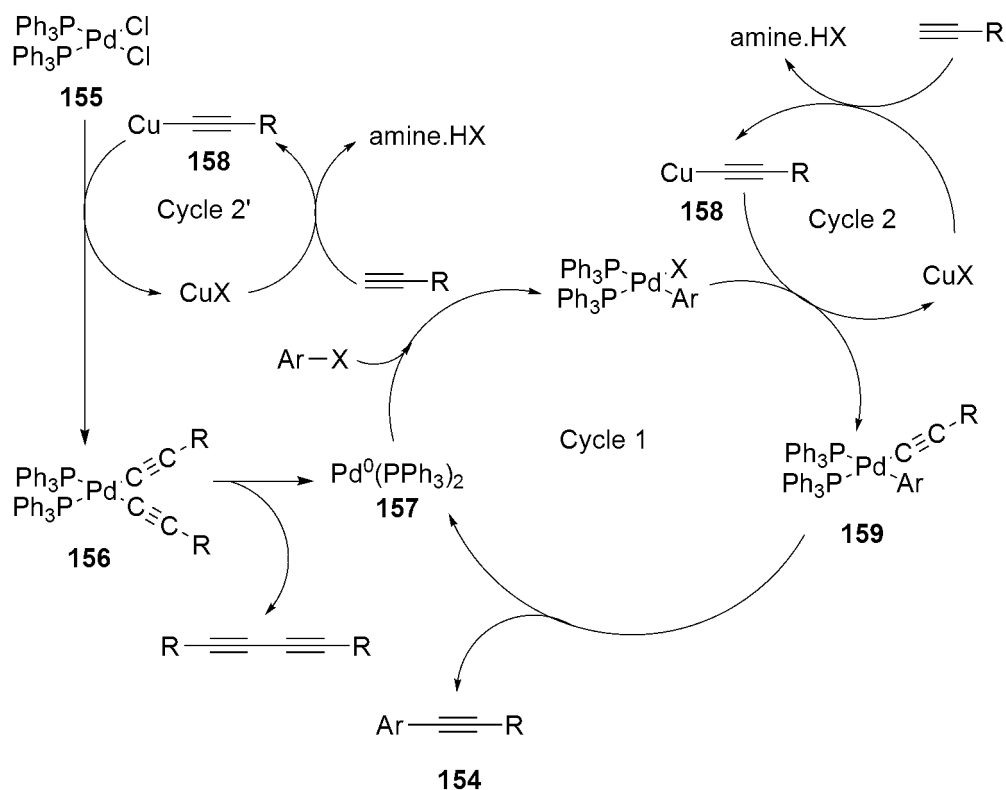
3.1 Introduction

The Sonogashira reaction was first reported in 1975, when Sonogashira, Heck and Cassar independently reported the palladium-catalysed reaction of aryl and vinyl halides with acetylene or monosubstituted alkynes to give acetylene derivatives **154** (**Scheme 75**, standard conditions).⁸⁴⁻⁸⁶ Sonogashira utilised a copper salt as a cocatalyst, analogous to a catalytic version of the Stephens-Castro reaction, which uses a stoichiometric copper acetylide.⁸⁷

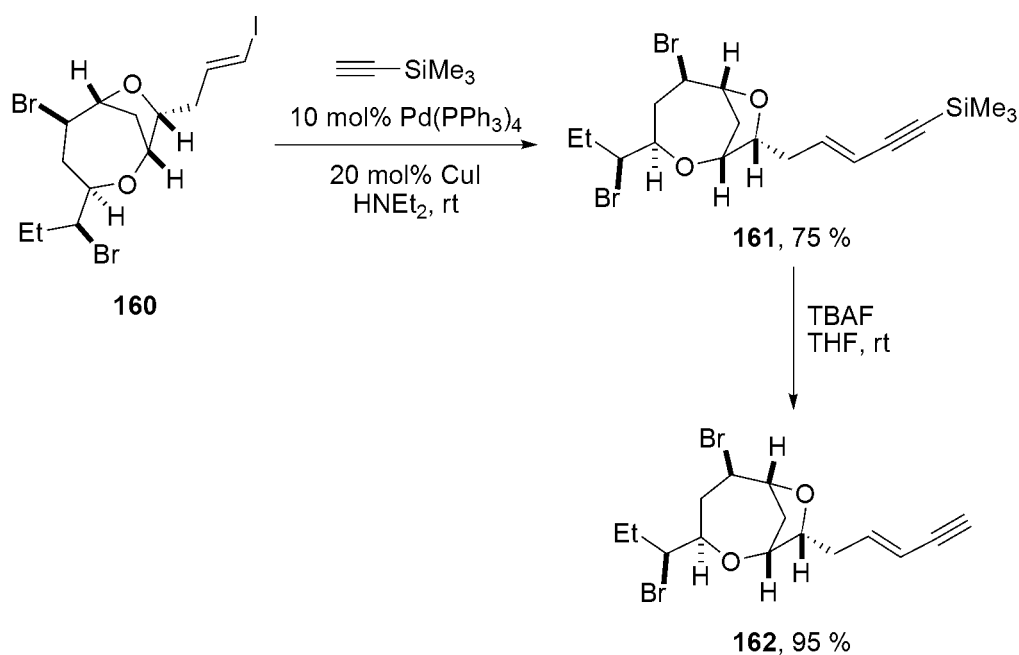


Scheme 75

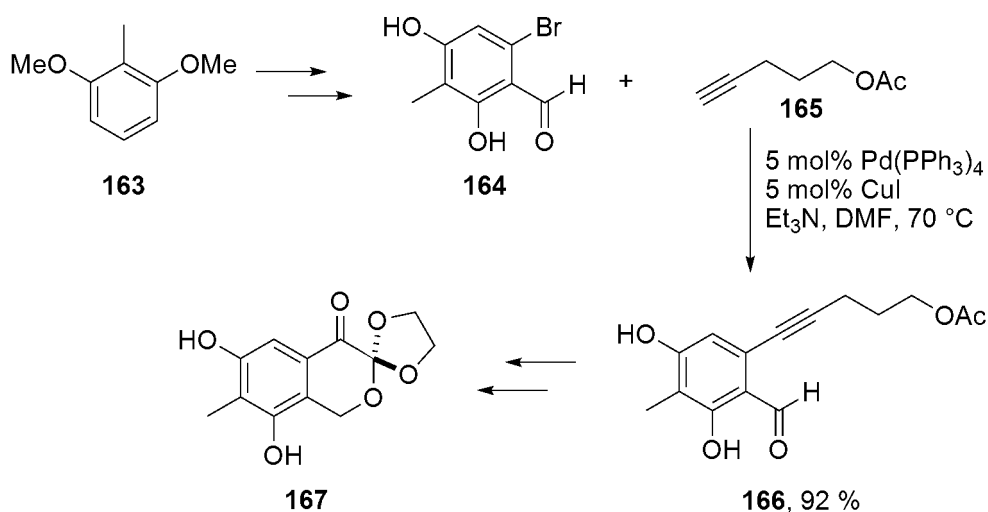
The mechanism of the Sonogashira reaction is not fully known, but the proposed mechanism is shown in **Scheme 76**.⁸⁸ Formation of the active catalyst is proposed to occur *via* transmetallation of precatalyst **155** (Cycle 2') and reductive elimination of the resulting complex **156** to give 14-electron species **157**. Oxidative addition of the halide electrophile to **157** is followed by transmetallation of the copper acetylide **158** formed in Cycle 2 to give species **159**. This then undergoes reductive elimination to yield the desired product **154** and regenerate the active catalyst **157** (Cycle 1). It is postulated that the copper acetylide is generated by abstraction by the amine of the acetylenic proton of a π -alkyne-copper complex, as the amines commonly employed in the reaction are not sufficiently basic to deprotonate the alkyne itself.



Acetylene derivatives are common in natural products and the Sonogashira reaction has been used in numerous total syntheses. The enyne moiety of red alga metabolite (-)-isoprelaufucin **162** was installed *via* a Sonogashira reaction of vinyl iodide **160** in 75 % yield (**Scheme 77**).⁸⁹ Removal of the silyl group of **161** with TBAF gave the natural product. Further manipulation of the C-C triple bond has also been exploited in natural product synthesis. For example, (±)-terreinol **167**, a metabolite of fungus *Aspergillus terreus*, has been synthesised from 2-methylresorcinol **163** *via* a cross-coupling between aryl bromide **164** and 4-pentynyl acetate **165** (**Scheme 78**).⁹⁰ The coupling proceeded to give 92 % yield of acetylene derivative **166**, which after alcohol protection and reduction of the aldehyde to a benzyl alcohol, underwent Pd-catalysed intramolecular cyclisation.

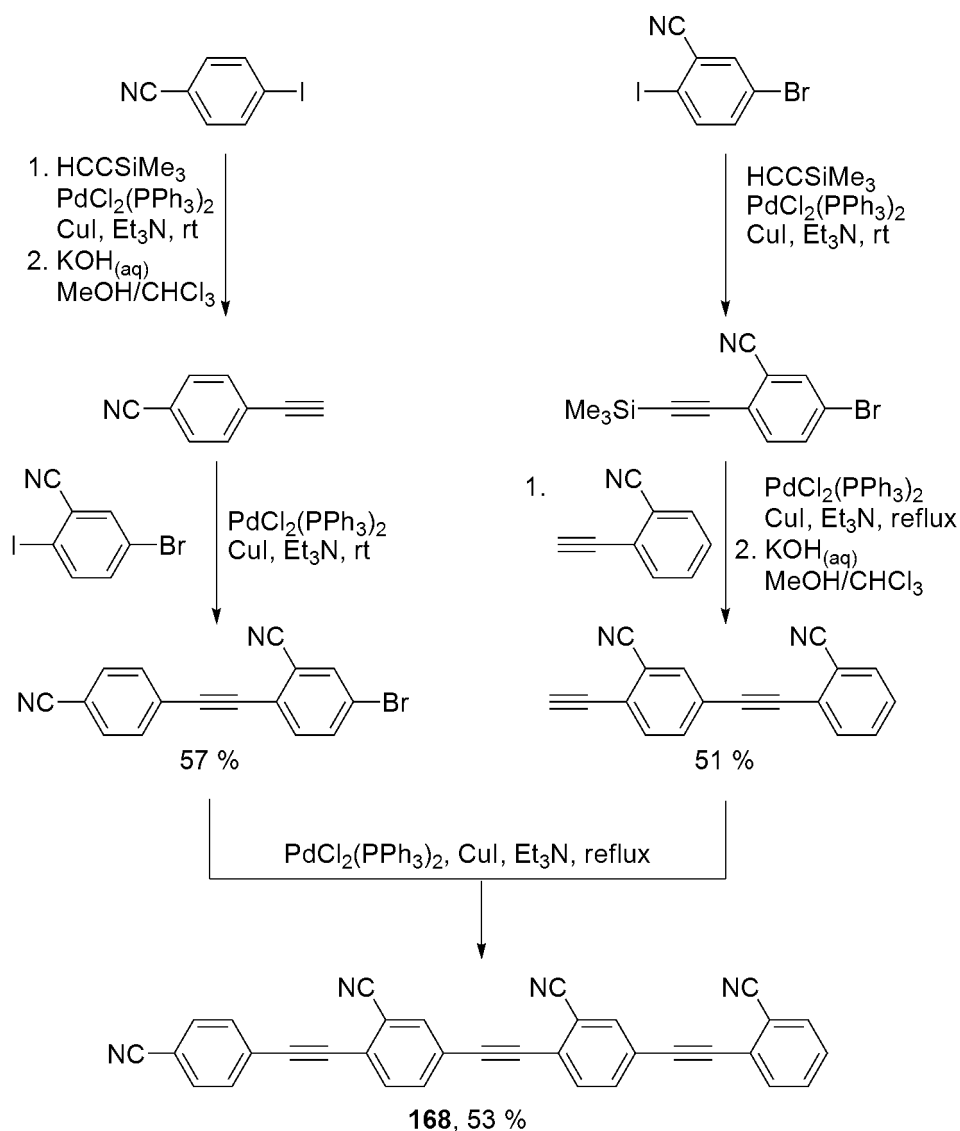


Scheme 77



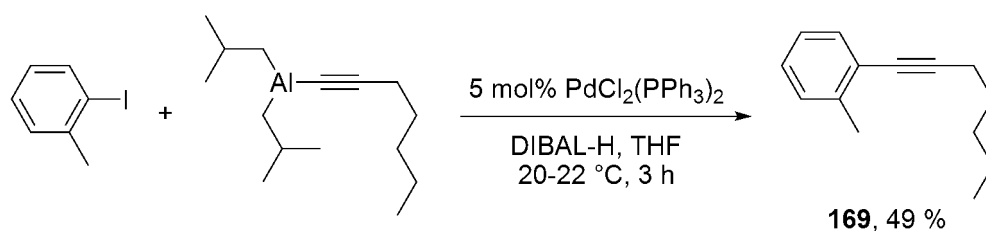
Scheme 78

Acetylene derivatives are also of importance in a wide range of materials chemistry applications. Extended conjugated systems featuring alternating aromatic rings and alkyne groups can act as organic semiconductors and molecular wires, in addition to having applications in LCD and light-emitting devices. Presently the Sonogashira reaction is usually employed in the synthesis of such molecules. For example, polycyano oligo(phenyleneethynylene) **168** has been synthesised using a convergent approach making use of several Sonogashira reactions (**Scheme 79**).⁹¹



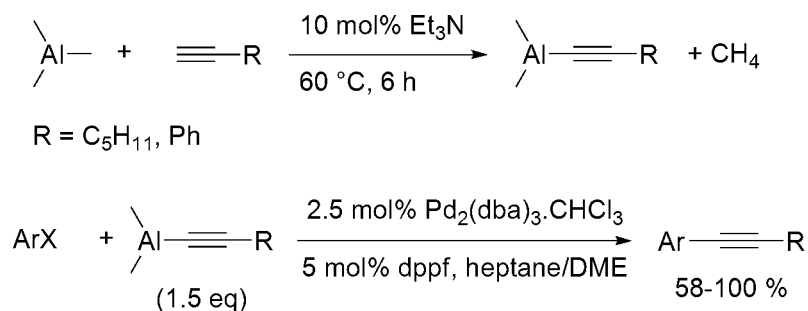
Scheme 79

Negishi first showed the potential of using alkynylaluminium reagents as an alternative to Sonogashira coupling in 1982.⁹² A sole example of the reaction between diisobutyl(1-heptynyl)aluminium and *o*-tolyl iodide was reported, giving 49 % yield of acetylene derivative **169** after 3 h at 20-22 °C in THF in the presence of a catalytic species generated from 5 mol% $\text{PdCl}_2(\text{PPh}_3)_2$ and DIBAL-H (**Scheme 80**).



Scheme 80

In 2004, Micouin showed that dimethylalkynylaluminium reagents, generated in a similar fashion to that described in Chapter 2, can be coupled to aryl and heteroaryl halides under palladium catalysis in good to excellent yields (**Scheme 81**).⁹³ Here the dialkylaluminium reagent was prepared by treatment of the alkyne with trimethylaluminium and 10 mol% triethylamine and was then used in the coupling reaction catalysed by $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ in conjunction with dppf in a mixture of heptane and DME. Selected results are shown in **Table 9**.



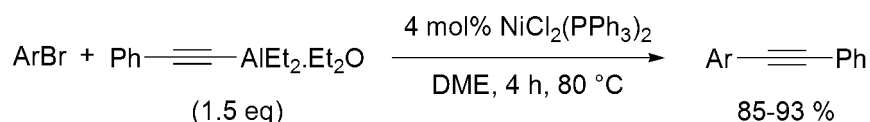
Scheme 81

Entry	R	ArX	T (°C)	Time (h)	Yield (%)
1	C ₅ H ₁₁	PhI	20	4.5	100
2	C ₅ H ₁₁	PhBr	85	5	87
3	C ₅ H ₁₁	PhCl	85	7	0
4	C ₅ H ₁₁	PhOTf	85	3	62
5	C ₅ H ₁₁	3-MeOC ₆ H ₄ I	20	3	100
6	C ₅ H ₁₁	4-MeO ₂ CC ₆ H ₄ I	20	4	90
7	C ₅ H ₁₁	4-MeOC ₆ H ₄ Br	85	4	90
8	C ₅ H ₁₁	3-MeOC ₆ H ₄ Br	85	4	89
9	Ph	PhI	20	6	100

10	Ph	2-BrC ₅ H ₄ N	85	1	92
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Table 9

Whilst our investigations were under way, Gau reported a nickel-catalysed approach.⁹⁴ Largely focussing on coupling of benzyl bromides with diethyl(phenylethynyl)aluminium, the NiCl₂(PPh₃)₂-catalysed coupling of aryl bromides with 1.5 equivalents of the same aluminium reagent was also reported, giving high yields (85-93 %) of acetylene derivatives after 4 h at 80 °C in DME (**Scheme 82**, **Table 10**). Here the alkynylaluminium reagent was prepared by deprotonation of the alkyne with ⁿBuLi, followed by transmetallation with diethylaluminium chloride, meaning lithium chloride is present in the reaction mixture. Diethyl ether was also added to the organoalane prior to cross-coupling.



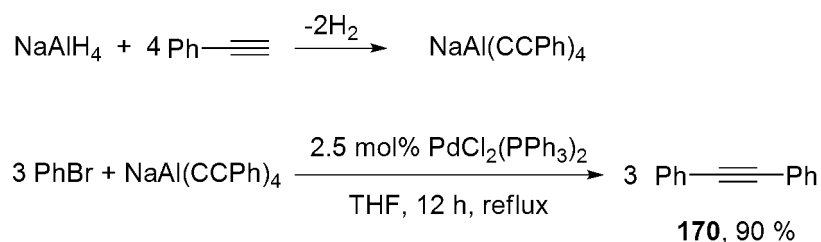
Scheme 82

Entry	Ar	Yield (%)
1	Ph	90
2	4-MeC ₆ H ₄	85
3	3,5-Me ₂ C ₆ H ₃	93
4	4-Me ₃ SiC ₆ H ₄	91
5	4-FC ₆ H ₄	92
6	4-NCC ₆ H ₄	85

Table 10

Sodium tetraalkynylaluminates, NaAl(CCR)₄, have also been employed in the synthesis of disubstituted acetylene derivatives. Blum has reported the use of these compounds, synthesised from sodium aluminium hydride and 4 equivalents of alkyne, in the PdCl₂(PPh₃)₂-catalysed reaction with aryl bromides (**Scheme 83**).⁹⁵ For example, diphenylacetylene **170** was synthesised

in 90 % yield from bromobenzene and sodium tetraphenylethynylaluminum after 12 h reflux in THF in the presence of 2.5 mol% Pd₂Cl₂(PPh₃)₂.



Scheme 83

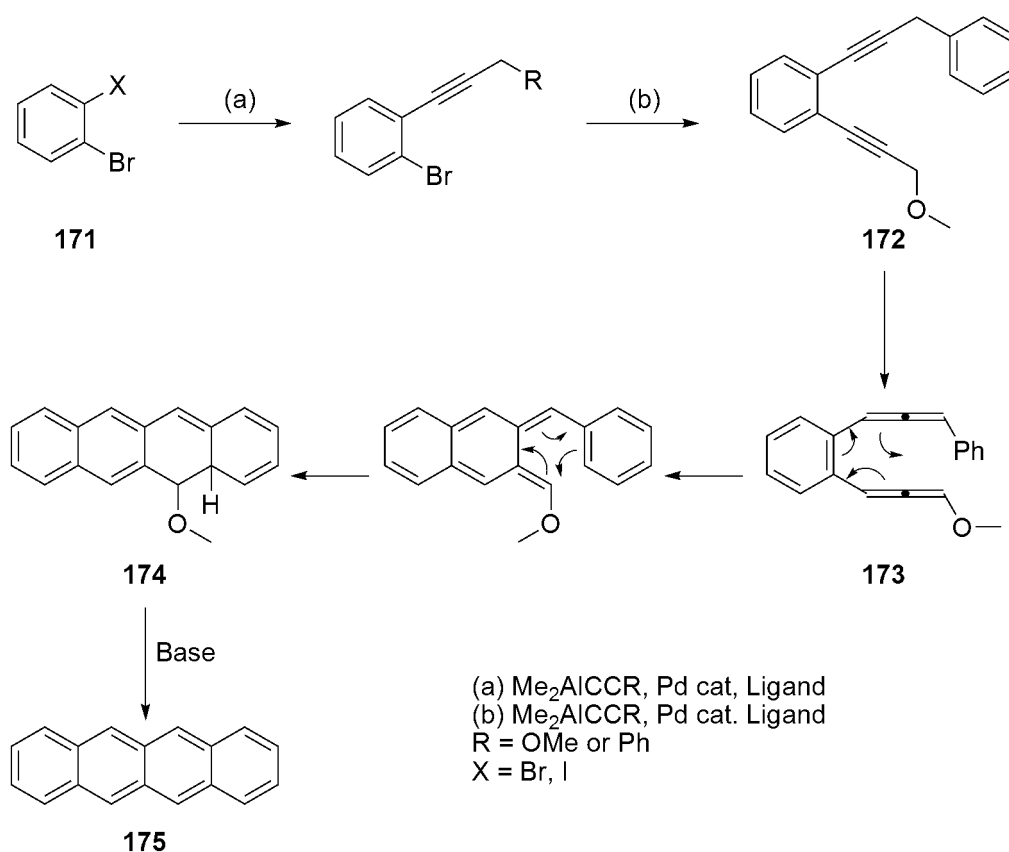
3.2 Aims and Objectives

Despite widespread use of the Sonogashira reaction, there remain several disadvantages requiring improvement.⁹⁶ For instance, copper salts are toxic to the environment, can be difficult to remove, and the *in situ* formation of copper acetylides can lead to undesired homocoupling of the alkyne. The reaction usually works best with electron-poor aryl or vinyl iodides, which are more expensive and less stable than the corresponding bromides. Deactivated, i.e. electron-rich, aryl bromides are challenging substrates, as are the less reactive aryl chlorides.

The initial aim of this work was to apply the dimethylalkynylaluminium reagents used in Chapter 2 to palladium-catalysed cross-coupling reactions. Although Micouin's existing precedent shows very high yields, in most cases dimethyl(1-heptynyl)aluminium was used in conjunction with aryl iodides. Only four reactions of dimethyl(phenylethynyl)aluminium **111** were reported, of which three were also with aryl iodides and one with 2-bromopyridine.⁹³ We hoped to expand on the applicability of this methodology and employ cheaper aryl bromides, and in addition optimise conditions for coupling to more challenging aryl chlorides and pseudohalides such as triflate and nonaflate.

Tetracenes represent another important area of research in materials chemistry, for their properties as organic semiconductors.⁹⁷ Once optimised, our aim was

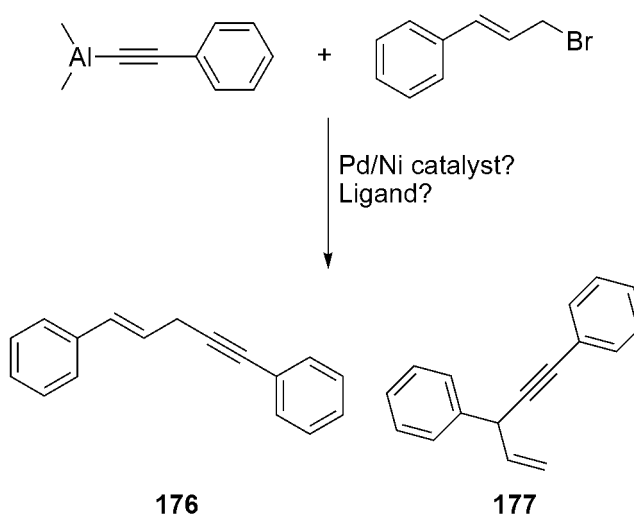
to utilise the cross-coupling methodology to provide a short, elegant synthesis of tetracene **175**. The proposed synthesis would start with 1,2-dihalobenzene **171**, with two sequential alkynylaluminium cross-coupling reactions leading to 1,2-dialkynylbenzene derivative **172** which could undergo isomerisation to bis-allene **173** (**Scheme 84**). Stepwise intramolecular electrocyclic ring closing reactions could lead to intermediate **174**, with elimination and aromatisation giving tetracene **175**.



Scheme 84

A further objective was to investigate the cross-coupling to allylic halides such as cinnamyl bromide. This would give interesting ‘skipped’ enyne compounds such as **176** and **177**, depending on α - or γ -attack on the allyl bromide (**Scheme 85**). Gamma-attack would furnish a stereocentre and, if product **177** could be synthesised selectively, an enantioselective route could be investigated using chiral ligands. The occurrence of this structural motif in natural products has been reported.⁹⁸ Existing syntheses utilise alkynyltin reagents, and Jeffery has reported a copper-catalysed reaction with

alkynylmagnesium bromide reagents.⁹⁹⁻¹⁰¹ A methodology avoiding the use of toxic tin compounds would be desirable.

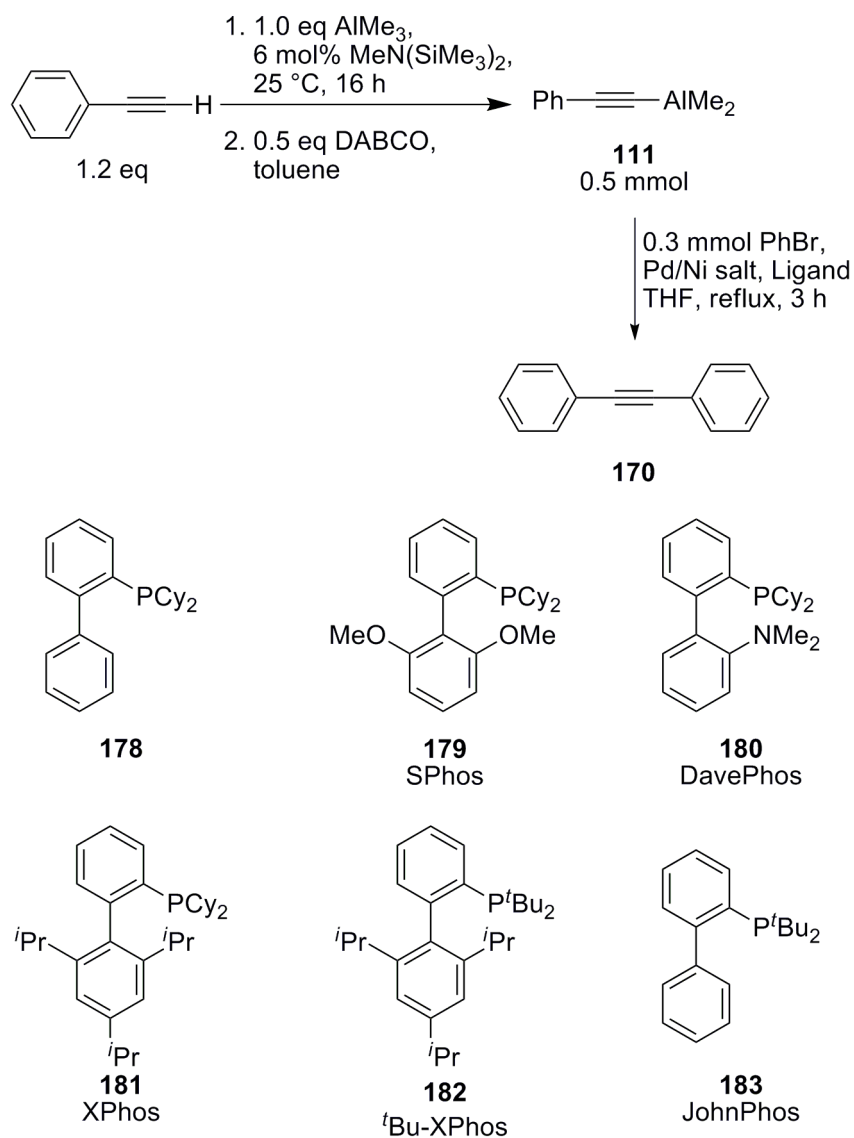


Scheme 85

3.3 Results and Discussion

3.3.1 Optimisation of Cross-Coupling to Aryl Bromides

Previous work within the Woodward group and others has found that palladium and nickel catalysts, particularly in combination with 1,1'-biphenylphosphine ligands, give excellent yields in the cross-coupling of aryl and vinyl halides and pseudohalides with alkylaluminium reagents.¹⁰² With this in mind, a range of palladium and nickel catalysts and phosphine ligands were screened in the reaction of bromobenzene with 1.6 equivalents of dimethyl(phenylethynyl)aluminium **111** in the presence of 0.5 equivalents of DABCO (**Scheme 86**). After 3 h in refluxing THF, the reaction was quenched and analysed by GC to give the results in **Table 11**. It can clearly be seen that $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ in combination with DavePhos **180** (entry **3**) gave the best result with a yield of 63 % and conversion of 80 %. The same catalyst with XPhos **181** also produced a useful result of 54 % yield with 91 % conversion. Indeed, in all cases where greater conversion was obtained, the yield of desired product was lower.



Scheme 86

Entry	Metal Salt ^a	Ligand ^b	Conversion (%) ^c	Yield (%) ^d
1	Pd ₂ (dba) ₃ ·CHCl ₃	178	69	51
2	Pd ₂ (dba) ₃ ·CHCl ₃	179	60	45
3	Pd ₂ (dba) ₃ ·CHCl ₃	180	80	63
4	Pd ₂ (dba) ₃ ·CHCl ₃	181	91	54
5	Pd ₂ (dba) ₃ ·CHCl ₃	182	71	15
6	Pd ₂ (dba) ₃ ·CHCl ₃	183	99	20
7	Pd(OAc) ₂	181	100	39
8	Pd(OAc) ₂	PPh ₃	52	35
9	PdCl ₂ (PPh ₃) ₂	N/A	51	38

10	NiCl ₂ (PPh ₃) ₂	N/A	0	0
11	NiCl ₂ (dppp) ₂	N/A	0	0
12	Pd(PPh ₃) ₄	N/A	53	39

^a Entries **1-6**, 1.5 mol%. Entries **7-12**, 3 mol%. ^b 3 mol%.

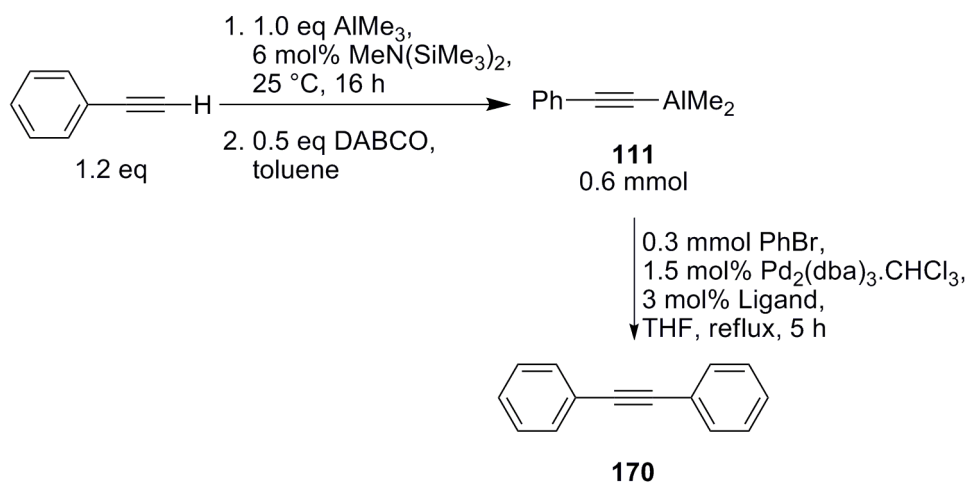
^c Based on depletion of starting material as determined by GC.

^d Determined by GC.

Table 11

It is notable that the nickel-catalysed reactions gave no reaction at all (entries **10** and **11**). This contrasts with the high yield reported by Gau at a similar temperature in DME.⁹⁴ THF is more strongly coordinating than DME, leading to a less reactive aluminium species, and Gau's conditions feature longer reaction time (4 h) and higher catalyst loading (4 mol%).

Increasing the reaction time to 5 h and using two equivalents of alkynylaluminium reagent drove the reaction to completion when catalysed by 1.5 mol% Pd₂(dba)₃·CHCl₃. Under these conditions, the effect of DABCO was studied with DavePhos and XPhos ligands (**Scheme 87**). It was found that DABCO was not of any benefit using DavePhos, with quantitative yield being obtained by GC, a slight improvement over 99 % yield obtained with DABCO present. On the other hand, when XPhos was used as the ligand, the yield increased from 91 to 98 % when DABCO was present (**Table 12**). Given that full consumption of starting material was seen in all cases, presumably XPhos generates a less selective Pd catalyst than DavePhos, and the addition of DABCO to moderate the reactivity of the alkynylaluminium reagent reduces unwanted side reactions.



Scheme 87

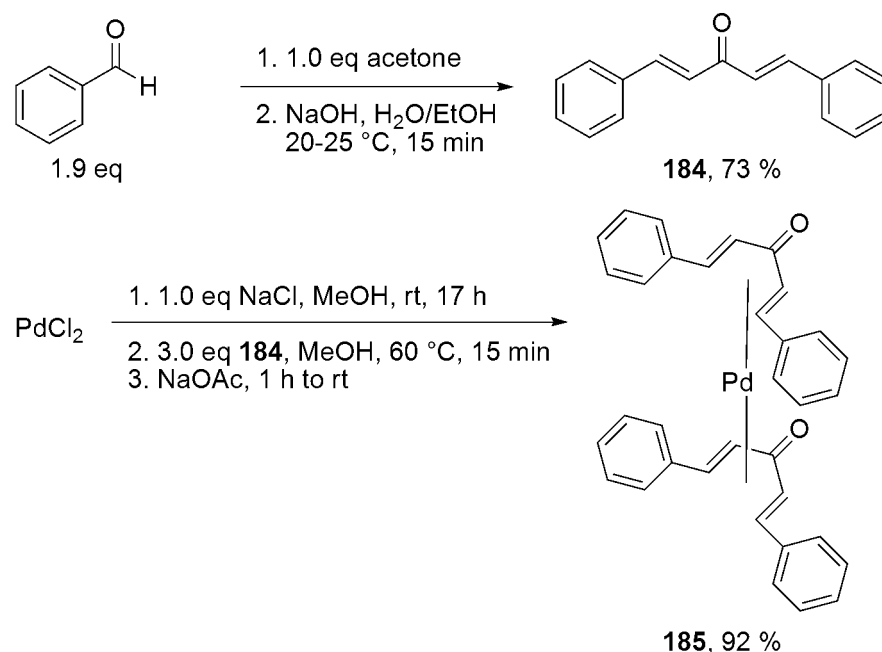
Entry	Ligand	DABCO	Conversion (%) ^a	Yield (%) ^b
1	DavePhos	Y	100	99
2	DavePhos	N	100	100
3	XPhos	Y	100	98
4	XPhos	N	100	91

^a Based on depletion of starting material as determined by GC.

^b Determined by GC.

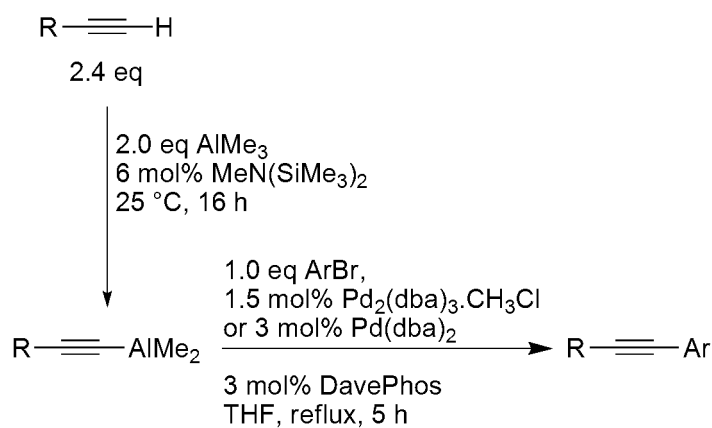
Table 12

It was found that $\text{Pd}(\text{dba})_2$ **185** was an equally suitable catalyst, doubling the catalyst loading to 3 mol% to maintain the overall palladium concentration. This catalyst was synthesised according to the preparation reported by Rettig and Maitlis (**Scheme 88**).¹⁰³ PdCl_2 and NaCl were stirred in methanol for 17 h at room temperature, after which the solution was diluted, freshly prepared dibenzylideneacetone **184** was added at 60 °C, and after 15 minutes NaOAc was added and the solution allowed to cool to room temperature over 1 h. Filtering off the precipitate afforded **185** in 92 % as a purple/brown powder.



Scheme 88

With optimal conditions found (**Scheme 89**), a range of examples were synthesised on a 1 mmol scale from different aryl bromides (**Table 13**, entries **1-12**). A series of compounds were also synthesised using dimethyl(1-octynyl)aluminium (**Table 13**, entries **13-21**). Isolated yields were generally good to excellent, for both electron-rich and electron-deficient electrophiles. Nitrogen-containing electrophiles were troublesome, with 2-bromopyridine giving an inseparable mixture containing 52 % yield of desired product (entry **11**), whilst 4-bromonitrobenzene failed to give any desired product (entry **12**). Benzyl acetylene also coupled in high yield to bromobenzene (91 %, entry **22**) with an identical yield when the reaction was run on double the scale (entry **23**).



Scheme 89

Entry	R	Ar	Catalyst	Yield (%) ^a
1	Ph	Ph	Pd ₂ (dba) ₃ ·CHCl ₃	95
2	Ph	4-MeOC ₆ H ₄	Pd ₂ (dba) ₃ ·CHCl ₃	88
3	Ph	4-CF ₃ C ₆ H ₄	Pd ₂ (dba) ₃ ·CHCl ₃	97
4	Ph	2-naphthyl	Pd ₂ (dba) ₃ ·CHCl ₃	69
5	Ph	2-FC ₆ H ₄	Pd ₂ (dba) ₃ ·CHCl ₃	65
6	Ph	3-MeOC ₆ H ₄	Pd ₂ (dba) ₃ ·CHCl ₃	86
7	Ph	3,5-Me ₂ C ₆ H ₃	Pd ₂ (dba) ₃ ·CHCl ₃	95
8	Ph	4-NCC ₆ H ₄	Pd ₂ (dba) ₃ ·CHCl ₃	84
9	Ph	3-NCC ₆ H ₄	Pd ₂ (dba) ₃ ·CHCl ₃	98
10	Ph	4-MeO ₂ CC ₆ H ₄	Pd(dba) ₂	96
11	Ph	2-pyridyl	Pd ₂ (dba) ₃ ·CHCl ₃	52 ^b
12	Ph	4-O ₂ NC ₆ H ₄	Pd ₂ (dba) ₃ ·CHCl ₃	0
13	C ₆ H ₁₃	Ph	Pd ₂ (dba) ₃ ·CHCl ₃	83
14	C ₆ H ₁₃	4-MeOC ₆ H ₄	Pd(dba) ₂	94
15	C ₆ H ₁₃	4-CF ₃ C ₆ H ₄	Pd(dba) ₂	92
16	C ₆ H ₁₃	2-FC ₆ H ₄	Pd(dba) ₂	67
17	C ₆ H ₁₃	3-MeOC ₆ H ₄	Pd(dba) ₂	87
18	C ₆ H ₁₃	3,5-Me ₂ C ₆ H ₃	Pd(dba) ₂	81
19	C ₆ H ₁₃	4-NCC ₆ H ₄	Pd(dba) ₂	82
20	C ₆ H ₁₃	3-NCC ₆ H ₄	Pd(dba) ₂	86
21	C ₆ H ₁₃	4-MeO ₂ CC ₆ H ₄	Pd(dba) ₂	58
22	C ₆ H ₅ CH ₂	Ph	Pd(dba) ₂	91

23	C ₆ H ₅ CH ₂	Ph	Pd(dba) ₂	91 ^c
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^a Isolated Yield.

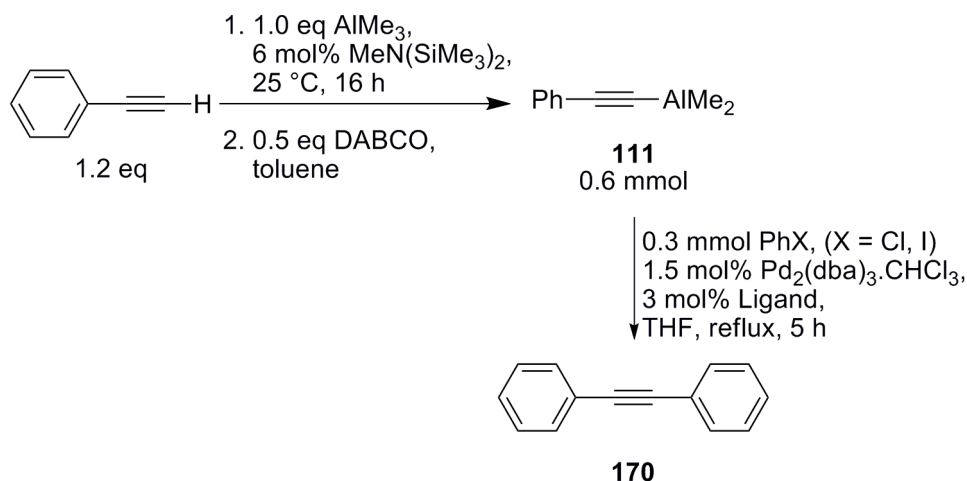
^b Yield determined by NMR of mixture obtained after column chromatography.

^c Performed on 2 mmol scale.

Table 13

3.3.2 Optimisation of Cross-Coupling to Other Aryl Halides and Pseudohalides

With the cross-coupling to aryl bromides working well, attention was turned to the optimisation of coupling to other aryl halides and pseudohalides such as triflate and nonaflate (**Scheme 90**). The optimised bromide coupling conditions were applied to couplings of dimethyl(phenylethynyl)aluminium **111** with iodo- and chlorobenzene, and the yield was determined by GC (**Table 14**). The coupling was also carried out with DABCO as an additive, and also using XPhos in place of DavePhos.



Scheme 90

Entry	Substrate	Ligand	DABCO	Conversion (%) ^a	Yield (%) ^b
1	PhI	DavePhos	N	100	94
2	PhI	DavePhos	Y	100	90
3	PhI	XPhos	N	100	58

4	PhI	XPhos	Y	100	93
5	PhCl	DavePhos	N	10	11
6	PhCl	DavePhos	Y	10	9
7	PhCl	XPhos	N	27	13
8	PhCl	XPhos	Y	100	40

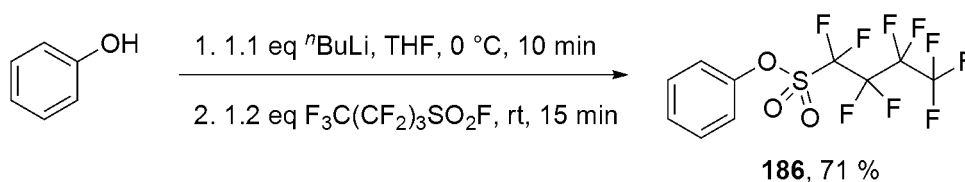
^a Based on depletion of starting material as determined by GC.

^b Determined by GC.

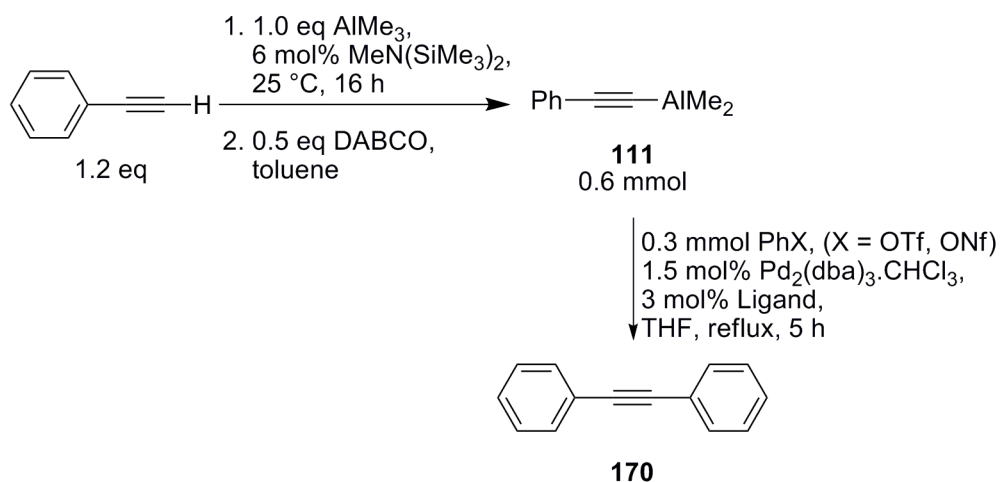
Table 14

It can be seen that under identical conditions, coupling to iodobenzene is comparable to that with bromobenzene (**Table 13**, entry **1** and **Table 14**, entry **1**). Again, addition of DABCO hinders the reaction using DavePhos as ligand, however, with XPhos there is a marked increase in yield from 58 to 93 %. As anticipated, coupling with chlorobenzene gave lower yields, although a best result of 40 % yield (entry **8**) using XPhos and DABCO was encouraging.

Similarly, coupling to the pseudohalides phenyl triflate and nonaflate was investigated in the same way (**Scheme 92**, **Table 15**). Commercial phenyl triflate was used, whilst the nonaflate **186** was synthesised in 71 % yield from phenol by deprotonation with ⁿBuLi in THF, followed by reaction with nonafluorobutanesulfonyl fluoride (**Scheme 91**), according to a procedure published by Oshima.¹⁰⁴ For both triflate and nonaflate, the standard aryl bromide coupling conditions proved to be most effective (**Table 15**, entries **1** and **5**) although lower yielding, with 66 and 60 % respectively.



Scheme 91



Scheme 92

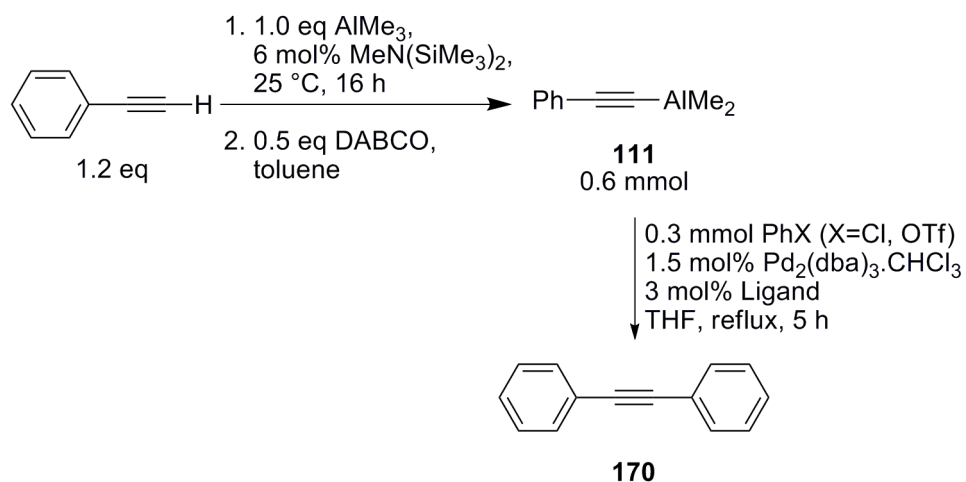
Entry	Substrate	Ligand	DABCO	Conversion (%) ^a	Yield (%) ^b
1	PhOTf	DavePhos	N	95	66
2	PhOTf	DavePhos	Y	98	49
3	PhOTf	XPhos	N	93	36
4	PhOTf	XPhos	Y	98	31
5	PhONf	DavePhos	N	100	60
6	PhONf	DavePhos	Y	100	48
7	PhONf	XPhos	N	100	37
8	PhONf	XPhos	Y	100	34

^a Based on depletion of starting material as determined by GC.

^b Determined by GC.

Table 15

In an effort to improve the yield of cross-coupling products, the effect of copper salts in the reactions with chlorobenzene and phenyl triflate was examined (**Scheme 93**), and the results are shown below (**Table 16**). As XPhos previously gave the best yield in the coupling with chlorobenzene, this was the only ligand used with this substrate (entries **1-6**), whilst both XPhos and DavePhos were used for coupling to the triflate (entries **7-12**). Unfortunately, the additives tested gave no improvement in reaction yield, compared to the results in **Tables 14** and **15**.



Scheme 93

Entry	PhX	Ligand	DABCO	Cu Salt	Conversion (%) ^a	Yield (%) ^b
1	PhCl	XPhos	Y	N/A	25	21 ^c
2	PhCl	XPhos	Y	Cu(TC)	1	1
3	PhCl	XPhos	Y	CuI	1	1
4	PhCl	XPhos	Y	Cu(TC)	0	0 ^c
5	PhCl	XPhos	Y	CuI	1	1 ^c
6	PhCl	XPhos	N	CuI	0	0
7	PhOTf	XPhos	N	CuI	23	10
8	PhOTf	XPhos	Y	CuI	34	24
9	PhOTf	XPhos	N	N/A	100	25 ^c
10	PhOTf	DavePhos	N	CuI	60	12
11	PhOTf	DavePhos	Y	CuI	58	55
12	PhOTf	DavePhos	N	N/A	100	44 ^c

^a Based on depletion of starting material as determined by GC.

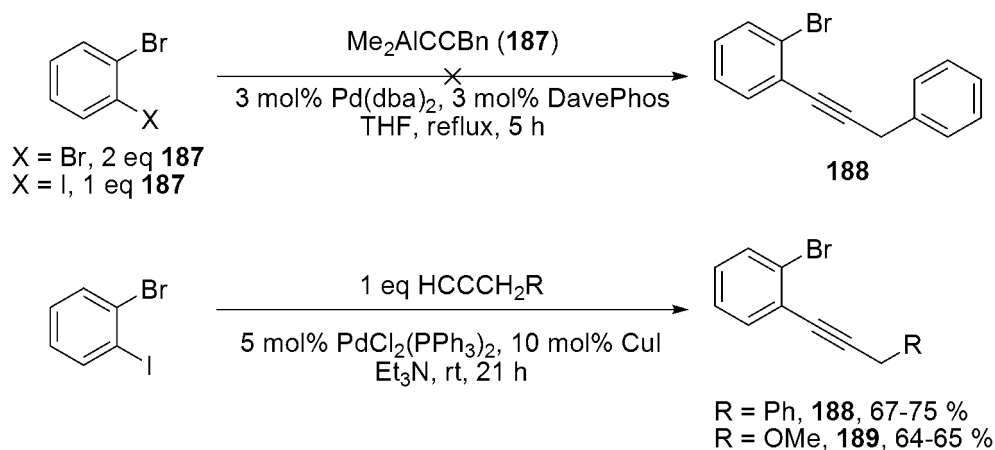
^b Determined by GC.

^c 3 mol% Pd₂(dba)₃·CHCl₃

Table 16

3.3.3 Towards the Synthesis of Tetracenes

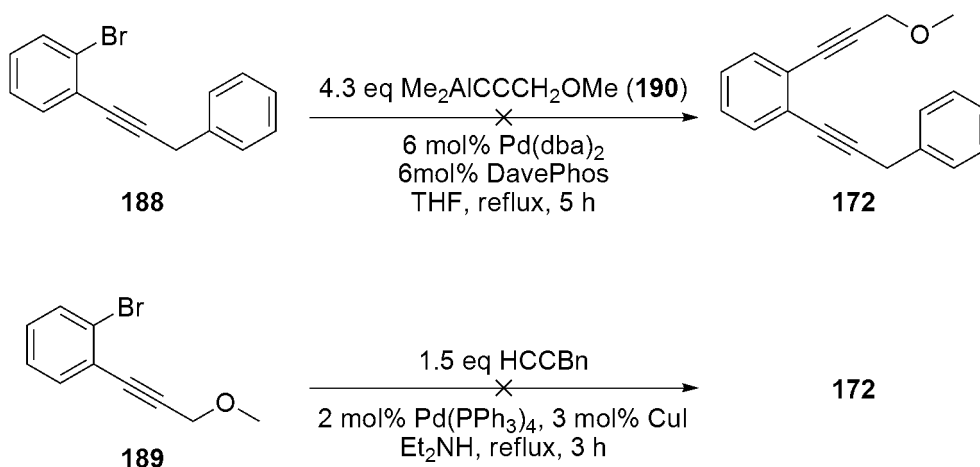
Initially, selective mono-alkynylation of 1,2-dibromobenzene with dimethyl(3-phenyl-1-propynyl)aluminium **187** was investigated using the optimised coupling conditions. After this proved unsuccessful, the coupling was repeated with 1-bromo-2-iodobenzene, with a similar outcome. A conventional Sonogashira coupling was instead used for the first coupling, with the intention of using alkynylaluminium cross-coupling to install the second alkynyl moiety. Sonogashira coupling was successful in adding each of the two alkynyl coupling partners individually to 1-bromo-2-iodobenzene, using a modification of a procedure reported by Storch (**Scheme 94**).¹⁰⁵ Thus, alkynyl halide **188** was synthesised in 75 % yield, which dropped slightly to 67 % when run on a larger scale. Methoxypropynyl bromobenzene **189** was also obtained in 64-65 % yield.



Scheme 94

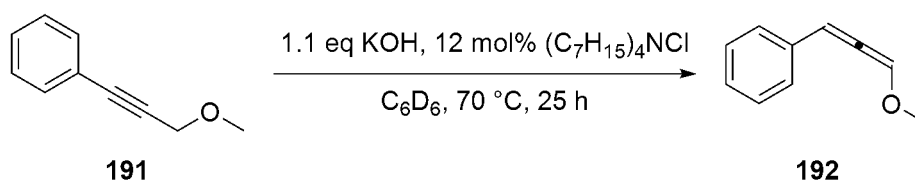
However, the attempt at coupling to alkynyl halide **188** using the alkynylaluminium reagent **190** was again unsuccessful, failing to yield diyne **172** (**Scheme 95**). The number of equivalents of alkynylaluminium, and the catalyst and ligand loading were increased to account for the steric hindrance of the 1,2-substitution pattern. A Sonogashira reaction between alkynyl halide **189** and 3-phenyl-1-propyne was also attempted, after the report of Just and Singh.¹⁰⁶ In this case no reaction occurred, and it seems likely that the steric

hindrance of the 1,2-substitution pattern is too great in these systems, and this approach to synthesising tetracenes was not pursued further.



Scheme 95

During these investigations, isomerisation of alkyne **191** to allene **192** was briefly studied, as a model for the more complex desired 1,2-dialkynylbenzene cross-coupling products (**Scheme 96**). Using a procedure reported by Arai and Shioiri, the alkyne was treated with potassium hydroxide and tetraheptylammonium chloride in C_6D_6 and heated at 70°C for 25 h, monitoring the reaction by NMR spectroscopy.¹⁰⁷ A yield of 33 % allene was observed after 2 h, although after 25 h only a trace amount was observed.

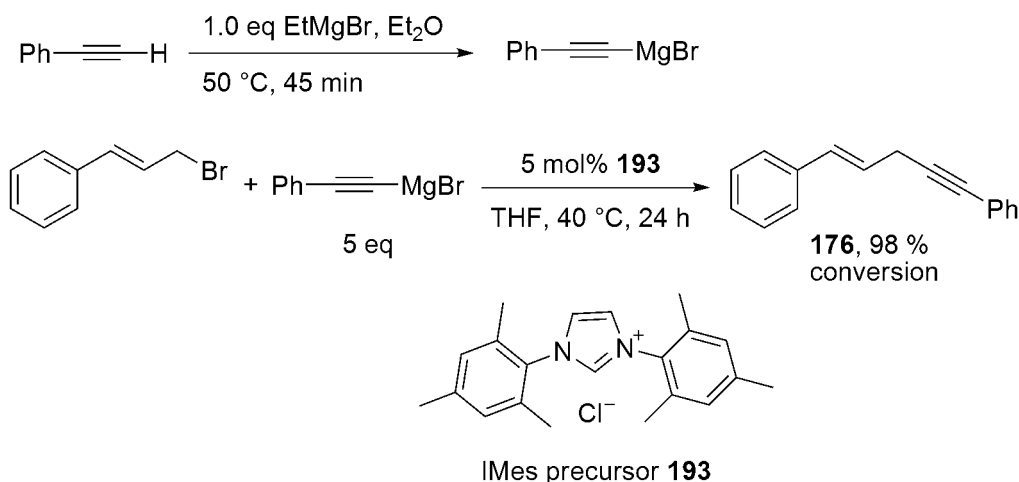


Scheme 96

3.3.4 Coupling to Cinnamyl Bromide

Cross-coupling between dimethylalkynylaluminium reagents and other halides were also of interest. Allyl halides were chosen as interesting substrates as potential coupling at the gamma position would generate a stereocentre. The coupling of dimethyl(phenylethynyl)aluminium **111** to cinnamyl bromide was

examined, although a range of conditions tested were all unsuccessful. However, on switching to phenylethynylmagnesium bromide, 24 % conversion to α -addition product **176** was observed after 18 h at 0 °C in THF, using 2.5 equivalents of Grignard reagent. The conversion increased to 82 % on addition of 5 mol% 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride **193** (which generates IMes *N*-heterocyclic carbene upon reaction with the Grignard reagent) and performing the reaction at 40 °C for 16 h. Extending the reaction time to 24 h and using 5 equivalents of PhCCMgBr gave 98 % conversion to **176** (Scheme 97). All conversions were measured by the ratio of cinnamyl bromide to α -addition product **176** in the crude ^1H NMR spectrum.



Scheme 97

The need for a large excess of alkynylmagnesium bromide would ideally require further optimisation to be synthetically useful, however due to time constraints this was not developed further.

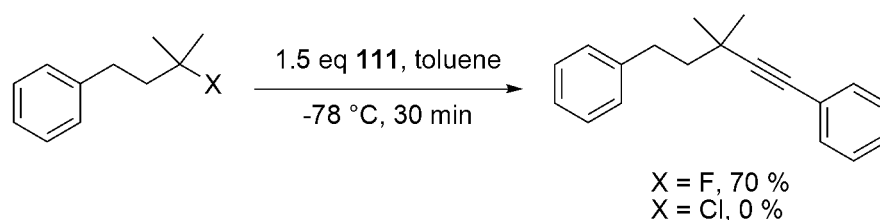
3.4 Conclusions

In conclusion, it was possible to couple dimethylalkynylaluminium compounds with a range of activated, unactivated and deactivated aryl bromides in good to excellent yields. Under the same conditions, coupling to an aryl iodide also proceeded in high yield. These results are comparable with those reported by Micouin and Gau, and in some cases the use of $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ or $\text{Pd}(\text{dba})_2$

and DavePhos gave improvements in yield.^{93,94} Phenyl triflate and nonaflate were also successfully coupled to dimethyl(phenylethynyl)aluminium in moderate yields, and on changing to XPhos and adding DABCO, chlorobenzene was also coupled, although further optimisation would be required for this to be synthetically useful. Sadly, this methodology could not be used in tetracene synthesis, and coupling to cinnamyl bromide was unsuccessful. Here alkynyl Grignard reagents were more successful, but at present a large excess of alkynylmagnesium bromide is required for high conversion, and the scope of the reaction was not investigated.

3.5 Future Work

An area where the use of these dialkylalkynylaluminium reagents could be investigated is in coupling to alkyl halides. Alkynylation of alkyl fluorides by dimethyl(phenylethynyl)aluminium **111** was reported to proceed in 70 % yield after 30 min at $-78\text{ }^{\circ}\text{C}$ in toluene by Maruoka (**Scheme 98**).¹⁰⁸ Under the same conditions, the chloride analogue failed to react, and the driving force of the reaction was attributed to the high affinity between aluminium and fluorine (*ca.* 664 kJmol^{-1} Al-F bond strength).



Scheme 98

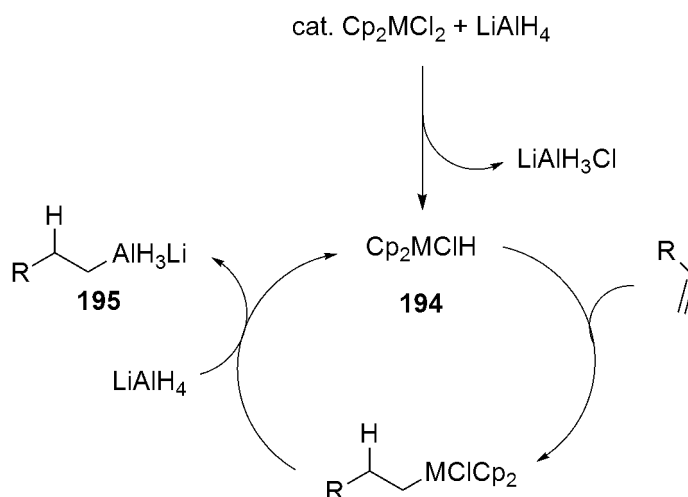
In addition, Sonogashira reactions to alkyl halides have been reported, utilising Pd-NHC complexes or nickel(II) pincer complexes.¹⁰⁹⁻¹¹¹ Trialkynylindium reagents have also been used in enantioselective nickel-catalysed cross-couplings to benzyl bromides.¹¹²

CHAPTER 4

Hydroalumination of Alkenes and Alkynes

4.1 Introduction

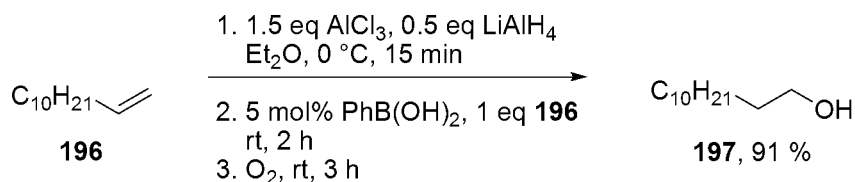
The catalytic hydroalumination of alkenes is a useful way to generate alkylaluminium reagents for use in an array of carbon-carbon bond forming reactions. A variety of aluminium hydride reagents can be used to achieve this, with LiAlH_4 or DIBAL-H affording efficient selective hydroalumination under mild conditions. Titanocene and zirconocene dichloride catalysts are common with LiAlH_4 , with initial hydrometallation of the alkene occurring by species **194** (Scheme 99).¹¹³ Transmetalation to aluminium then affords alkylaluminium reagent **195** and regenerates metal hydride **194**. Lee reported the only use of catalytic $\text{Cp}^*_2\text{ZrCl}_2$ in hydroalumination methodology, for the hydroalumination of alkenes, while no studies of alkynes with this catalyst have been reported.¹¹⁴



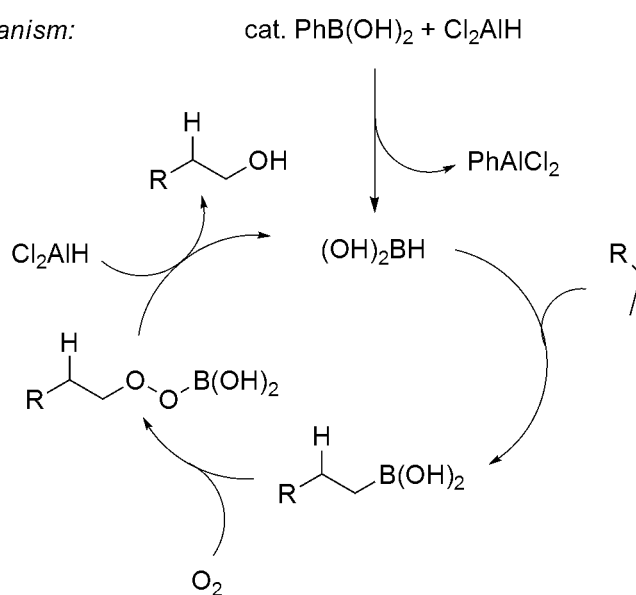
Scheme 99

Ashby has reported the use of chloroalanes and amidoalanes of the type $\text{HAl}(\text{NR}_2)_2$ with catalytic titanocene dichloride for the hydroalumination of a range of alkenes.¹¹⁵ Yamamoto showed hydroalumination with dichloroalane generated *in situ* can be achieved using an organoborane catalyst, for example giving 1-dodecanol **197** in 91 % yield from 1-dodecene **196** after an O_2 quench (Scheme 100).^{116,117} This has been postulated to proceed *via* reaction of the alane with the organoborane catalyst to form a B-H bond. This is followed by hydroboration of the C-C double bond, with the resulting alkylborane reacting

with O₂ to give an alkylperoxy borane species. Reduction with dichloroalane then gives alcohol **197** and regenerates (OH)₂BH, completing the catalytic cycle.

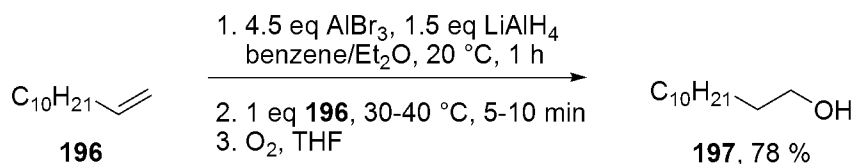


Proposed Mechanism:



Scheme 100

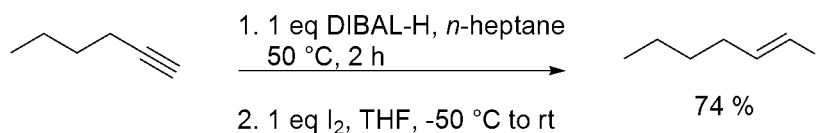
Gorobets has used a heterogeneous LiAlH₄·3AlBr₃ system to generate *in situ* dibromoalane. The above transformation on alkene **196** was achieved using this approach with 78 % **197**, without the need for a hydroalumination catalyst (**Scheme 101**).¹¹⁸



Scheme 101

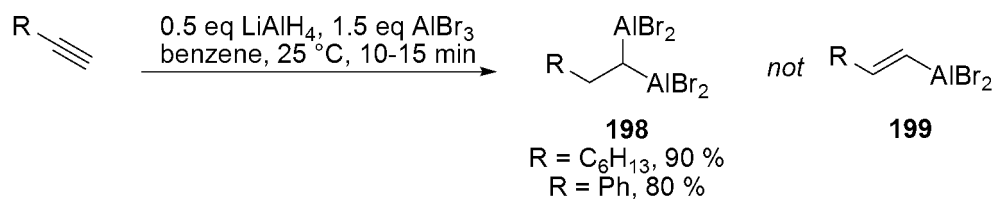
The hydroalumination of alkynes using DIBAL-H was reported by Zweifel in 1967 (**Scheme 102**).¹¹⁹ Since then, this approach has seen widespread use.

Amidoalanes can also be used to give selective hydroalumination of internal alkynes, however, hydroalumination of terminal alkynes results in *ca.* 1:1 mixtures of alkyl and alkenyl aluminium reagents.¹²⁰



Scheme 102

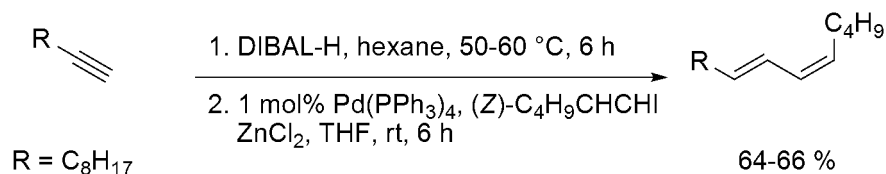
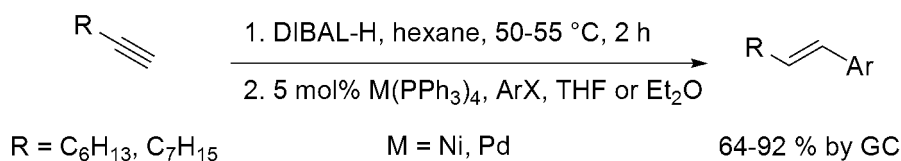
The use of dihaloalanes has been underexploited in this area. Dichloroalane has been used to reduce alkynylphosphates to alkynylphosphines, rather than hydroaluminate the C-C triple bond.¹²¹ Gorobets also used the LiAlH₄·3AlBr₃ system in benzene or toluene to hydroaluminate alkynes, generating alkyl dialuminium species **198** rather than vinylaluminium species **199** (**Scheme 103**).¹²²



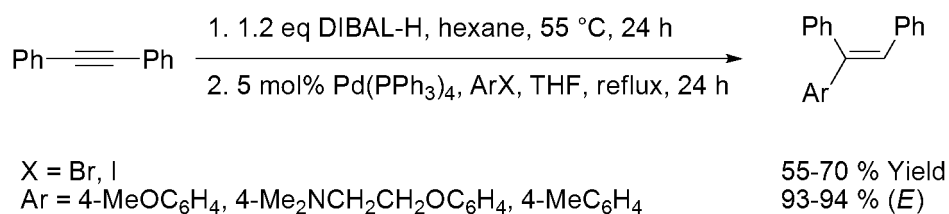
Scheme 103

As an aluminium analogue to Suzuki boronic acid coupling, the palladium-catalysed cross-coupling of DIBAL-H-derived vinylalanes to aryl halides has been reported very rarely.¹²³ Negishi has employed vinylalanes in nickel- and palladium-catalysed cross-coupling reactions with aryl and vinyl halides (**Scheme 104**).^{124,42} In addition, Al-Hassan used diisobutylvinylaluminium reagents obtained from diphenylacetylene to give triaryl-substituted alkenes.¹²⁵ There are, however, several drawbacks associated with this methodology: its limitation to alkyl or internal aryl alkynes, the high pyrophoricity of neat DIBAL-H, and the presence of bulky isobutyl groups which can hinder transmetalation to catalysts, giving slow or no reaction.

Negishi:



Al-Hassan:



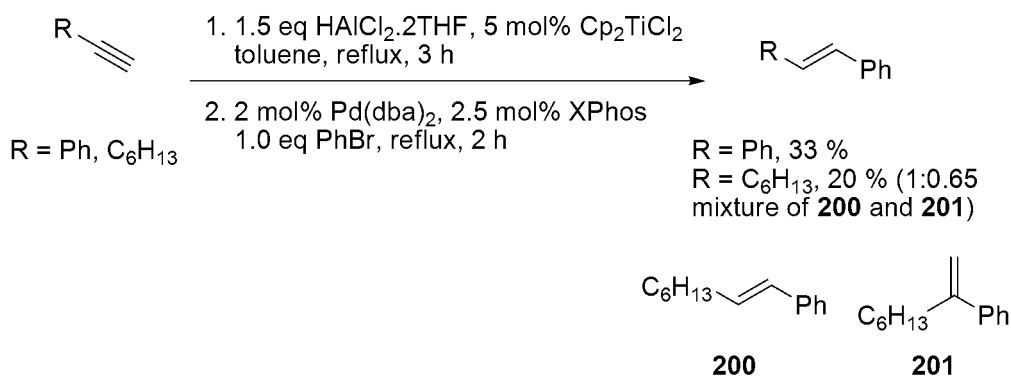
Scheme 104

4.2 Aims and Objectives

Initially, the objective of this work was to develop a practical method of dibromoalane hydroalumination of alkenes and alkynes, with the aim of avoiding the need for transition metal catalysis. It was envisaged that the resulting organoaluminium species could be used in a range of synthetic applications such as reaction with aldehydes and ketones to generate chiral propargylic alcohols, conjugate addition to enones and cross-coupling with aryl halides.

Gorobets' use of a $\text{LiAlH}_4\text{-AlBr}_3$ mixture to generate dibromoalane *in situ* was of interest in this regard.¹¹⁸ Investigation of the $\text{LiAlH}_4\text{-MeOH}$ mixture reported by Lee as a mild reducing agent in the Cp_2TiCl_2 -catalysed hydroalumination of alkynes was another objective, as if successful, the resulting products could be utilised in carbon-carbon bond forming reactions.¹²⁶

Recent work within the Woodward group found that the Cp_2TiCl_2 -catalysed hydroalumination of alkynes by the THF adduct of dichloroalane proceeds with high selectivity and the resulting vinylalanes can be coupled to bromobenzene (**Scheme 105**). Modest yields of (*E*)-alkene product were obtained in the presence of a $\text{Pd}(\text{dba})_2/\text{XPhos}$ catalyst system. Our objective became therefore to optimise both the hydroalumination and cross-coupling steps to obtain a synthetically useful, selective procedure. There exists only one previously reported use of a haloalane THF adduct as a synthetic reagent.¹²⁷ Brown has shown diethyl ether and THF adducts of dichloroborane give hydroboration products of alkenes and alkynes.¹²⁸



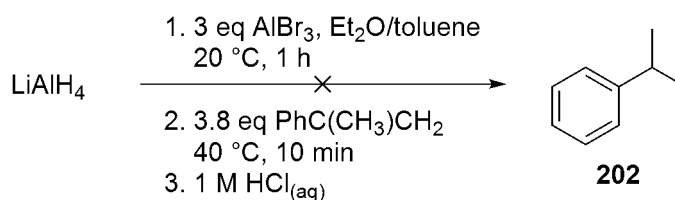
Scheme 105

A further aim was to investigate the reactivity of organoaluminium species involved in the cross-coupling reactions of both vinyl- and alkynylaluminium reagents, by way of molecular modelling, in order to gain an understanding of the relative reactivity of these species and also DABAL- Me_3 .

4.3 Results and Discussion

4.3.1 Alkene Hydroalumination

An initial attempt at hydroalumination using Gorobets' $\text{LiAlH}_4 \cdot 3\text{AlBr}_3$ conditions was made on α -methylstyrene (**Scheme 106**).¹¹⁸ Formation of 2-phenylpropane **202** was unsuccessful, so the simpler substrates 1-decene and 1-dodecene were studied.

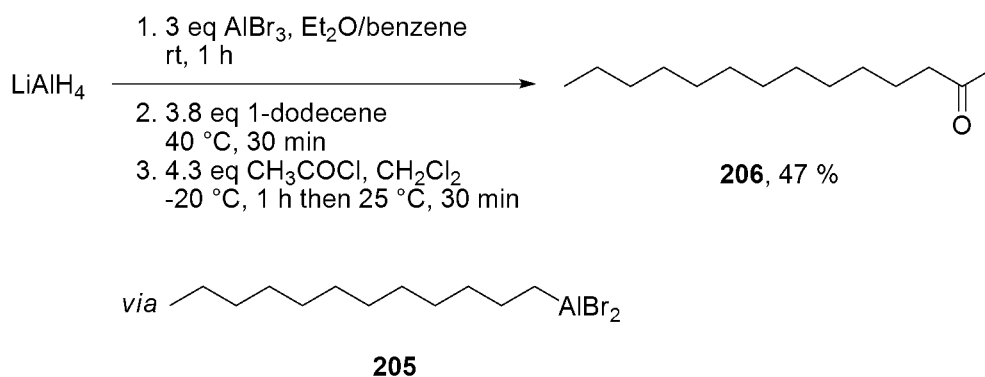


Scheme 106

Many attempted reactions proved unsuccessful, suffering from Friedel-Crafts side reactions between benzene and aluminium species or issues of selectivity for one end of the alkene double bond. However, complete conversion to decane **203** was observed by NMR spectroscopy on the crude reaction products when 1-decene was treated with the $\text{LiAlH}_4 \cdot 3\text{AlBr}_3$ mixture. In this case the reaction was run in hexane by adding a solution of AlBr_3 in hexane to solid LiAlH_4 and heating the mixture at 40°C for 15 min.

The deuterium incorporation upon quenching the hydroalumination of 1-dodecene with D_2O was then measured by GC-MS. Here Gorobets' conditions were utilised, with the modification of using a 6 M slurry of LiAlH_4 in Et_2O and extending the reaction time with the alkene to 30 min. Incorporation in the $(1\text{-}^2\text{H})$ dodecane **204** was determined to be 62 %.

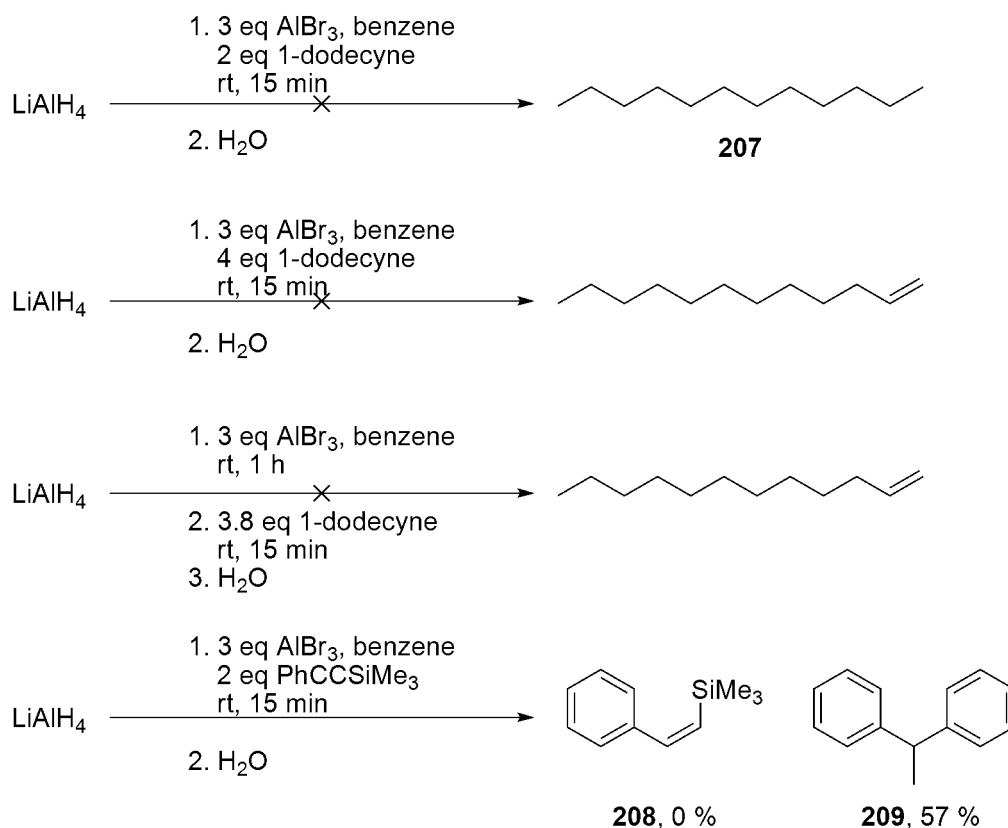
Some success was achieved in the reaction of dodecylaluminium reagent **205** with acetyl chloride (**Scheme 107**). Using the same conditions as above, the resulting hydroalumination mixture was reacted with acetyl chloride at -20°C , and after stirring at this temperature for 1 h, and a further 30 min at 25°C , a 47 % yield of ketone **206** was obtained.



Scheme 107

4.3.2 Alkyne Hydroalumination

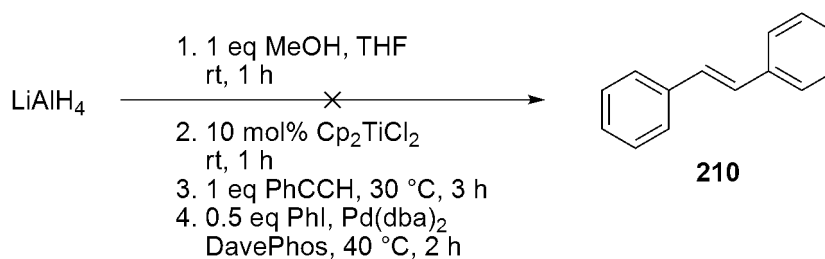
Gorobets' *in situ* dibromoalane conditions for the hydroalumination of alkynes were used in an attempt to convert 1-dodecyne to dodecane **207** (**Scheme 108**).¹²² With the aim of selective hydroalumination to the vinylaluminum, the stoichiometry of the reaction was changed to a 1:1 ratio of alkyne to HAlBr_2 . Gorobets' alkene hydroalumination conditions were also trialled, but unfortunately none of these reactions were successful. Switching to 1-phenyl-2-trimethylsilylacetylene afforded a yield of 57 % 1,1-diphenylethane **209**, rather than desired alkene **208**, by NMR spectroscopy of the crude product. It is believed this was generated by silicon direction of the aluminium reagent to the phenyl end of the alkyne, followed by Friedel-Crafts reaction with benzene and subsequent loss of the silyl group.



Scheme 108

4.3.3 Development of Vinylaluminium Cross-Coupling

The titanocene dichloride-catalysed $\text{LiAlH}_4/\text{MeOH}$ hydroalumination of alkynes reported by Lee was investigated (**Scheme 109**).¹²⁶ Starting with phenylacetylene, the reaction was carried out at 30 °C for 3 h in THF, and a portion of the resulting mixture (2.0 equivalents) was then treated with iodobenzene (1.0 equivalent), $\text{Pd}(\text{dba})_2$ and DavePhos (both 3 mol%). This attempt at vinylalane cross-coupling however failed to give (*E*)-stilbene **210**, affording mostly unreacted alkyne and a mixture of hydroalumination products.

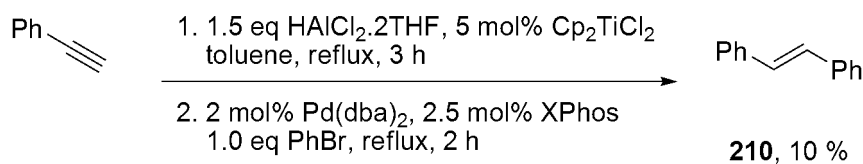


Scheme 109

Dichloroalane(bis-tetrahydrofuran) adduct **211** was synthesised from LiAlH_4 and AlCl_3 in good yield (71 %) using the procedure reported by Schmidt and Flagg (**Scheme 110**).¹²⁹ Addition of THF to the Et_2O solution of dichloroalane caused precipitation of the desired adduct. Evolution of H_2 gas upon hydrolysis was used to confirm the molarity of active hydrogen present. The Woodward group's initial hydroalumination-cross-coupling reaction conditions were reproduced to give (*E*)-stilbene **210** in 10 % yield, accompanied by several mixed fractions also containing the desired product (**Scheme 111**).

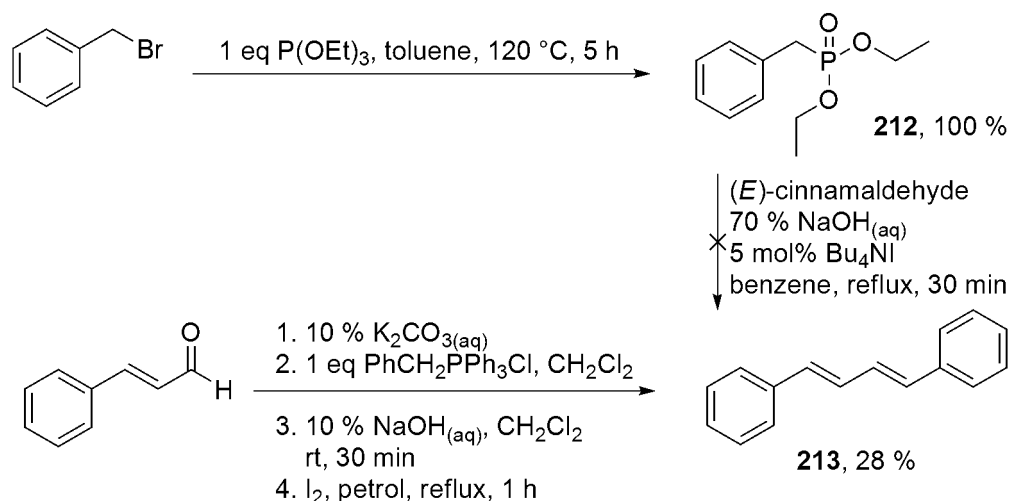


Scheme 110



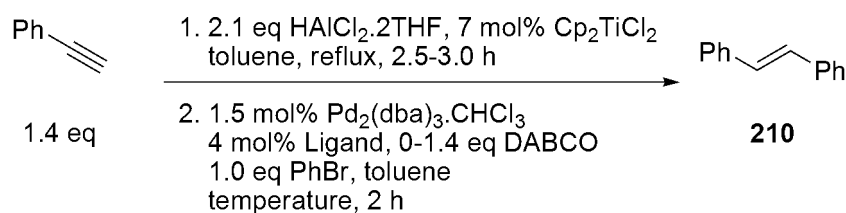
Scheme 111

In order to optimise this process rapidly by determination of conversion and yield by GC, it was necessary to synthesise potential by-product diene **213**. Benzyl bromide was first converted to benzyl phosphonate **212** in quantitative yield by reaction with triethyl phosphite at 120 °C for 5 h in toluene (**Scheme 112**).¹³⁰ Sadly the Horner-Wadsworth-Emmons reaction required to yield diene **213** gave only a 2:1 mixture of phosphonate to product, so a Wittig reaction of cinnamaldehyde and benzyltriphenylphosphonium chloride was employed instead.¹³¹ Purification problems meant that a low yield of 28 % of diene **213** was obtained, although this was sufficient for GC calibration.



Scheme 112

A range of conditions for both the hydroalumination of phenylacetylene and the subsequent vinylalane cross-coupling to bromobenzene were then screened (**Scheme 113**, **Table 17**). In all cases the ratio of vinylalane to aryl bromide was increased to 1.4:1 and cross-coupling catalyst and ligand loading was increased to 1.5 mol% (3 mol% effective Pd) and 4 mol% respectively. The addition of DABCO (0.5 eq wrt vinylalane) saw the yield of stilbene increase to 83 % (entry **2**), and optimal conditions were found when the cross-coupling was run at 80 °C (entry **9**). Further increases in the amount of DABCO added, and further decreases in cross-coupling temperature gave lower yields. Changing the ligand to DavePhos saw no real advantage over XPhos.



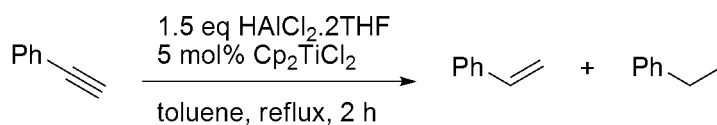
Scheme 113

Entry	Time (h)	eq DABCO	Temperature (°C)	Ligand	Yield Stilbene (%) ^a	Yield Diene (%) ^a
1	2.5	0.00	110	XPhos	54	3
2	2.5	0.70	110	XPhos	83	3
3	2.5	0.00	110	DavePhos	56	4
4	3.0	0.00	110	XPhos	59	4
5	3.0	1.12	110	XPhos	25	4
6	3.0	1.40	110	XPhos	29	3
7	3.0	0.00	50	XPhos	40	1
8	3.0	0.00	rt	XPhos	6	3
9	3.0	0.70	80	XPhos	86	1

^a GC Yield.

Table 17

The optimal reaction time for the hydroalumination by $\text{HAlCl}_2 \cdot 2\text{THF}/\text{Cp}_2\text{TiCl}_2$ was also investigated by GC after proton quench (**Scheme 114**, **Table 18**). Hydroalumination of phenylacetylene was carried out in refluxing toluene with 1.5 eq $\text{HAlCl}_2 \cdot 2\text{THF}$ and 5 mol% Cp_2TiCl_2 . A reaction time of 1 h was most effective and minimised the amount of over-hydroalumination to ethylbenzene (entry 2).



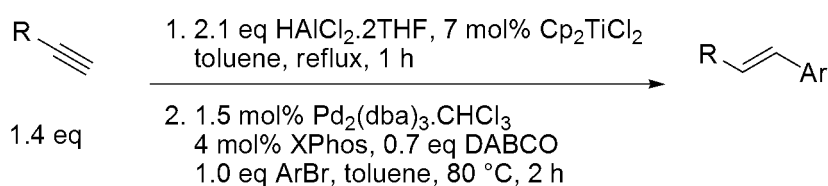
Scheme 114

Entry	Time (h)	PhCCH (%) ^a	PhCH=CH ₂ (%) ^a	PhCH ₂ CH ₃ (%) ^a
1	0.5	1	76	23
2	1.0	1	79	20
3	2.0	1	77	22

^a GC Yield.

Table 18

With a high GC yield of the desired cross-coupling product obtained, a range of examples were synthesised (**Scheme 115**, **Table 19**). Unfortunately, there was a wide discrepancy between isolated yields and those measured by GC analysis of duplicate reactions. Use of 3,3-dimethyl-1-butyne gave improved isolated yields (entries **12-17**), comparable with GC data. The low yields were therefore attributed to interactions of the stilbene derivatives with toluene causing separation issues in flash column chromatography and filtration.



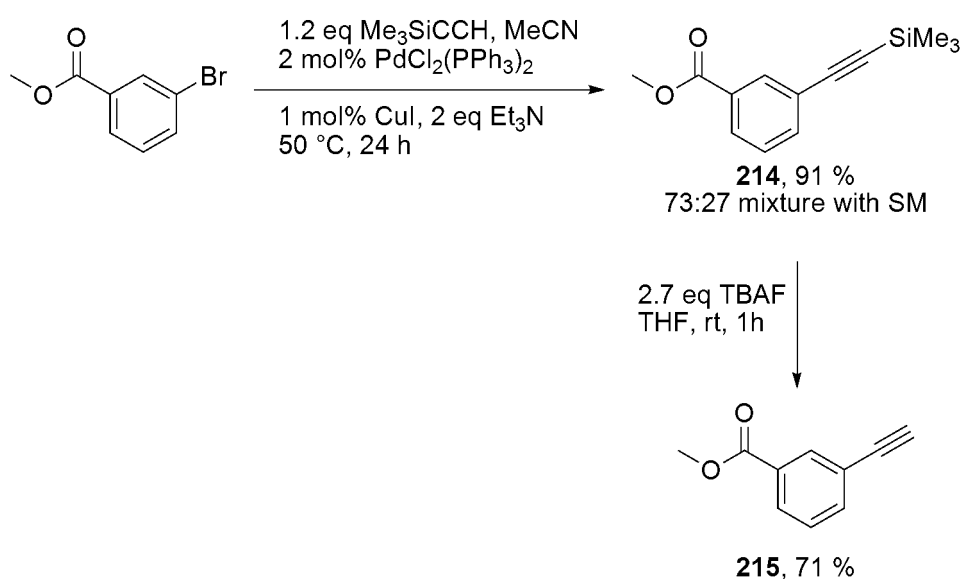
Scheme 115

Entry	R	Ar	Isolated Yield (%)	GC Yield (%)
1	Ph	Ph	41	86
2	Ph	Ph	55	N/A
3	Ph	3,5-Me ₂ C ₆ H ₃	28	65
4	Ph	4-F ₃ CC ₆ H ₄	48	70
5	Ph	4-MeO ₂ CC ₆ H ₄	43	68
6	4- ^t BuC ₆ H ₄	Ph	34	72
7	4- ^t BuC ₆ H ₄	4-F ₃ CC ₆ H ₄	23	74
8	Ph	3-NCC ₆ H ₄	25	N/A
9	Ph	Ph	37	N/A
10	3-MeO ₂ CC ₆ H ₄	Ph	0	N/A
11	3-HOC ₆ H ₄	Ph	0	N/A
12	^t Bu	Ph	67	N/A
13	^t Bu	3,5- Me ₂ C ₆ H ₃	50	N/A
14	^t Bu	4-F ₃ CC ₆ H ₄	79	75
15	^t Bu	4-MeO ₂ CC ₆ H ₄	78	N/A
16	^t Bu	3-MeOC ₆ H ₄	85	N/A

17	^t Bu	3-C ₄ H ₃ S	41	N/A
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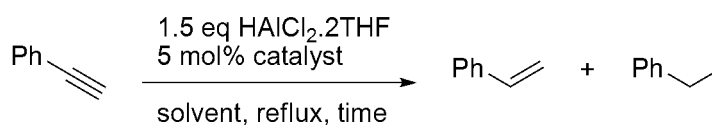
Table 19

To obtain ester-substituted phenylacetylene **215** for cross-coupling (**Table 19**, entry **10**), silyl acetylene **214** was first synthesised from methyl 3-bromobenzoate in a Sonogashira reaction (**Scheme 116**).¹³² This was achieved with 91 % yield of a 73:27 mixture of **214** and the bromide starting material. Carrying this mixture forward, the silyl acetylene was deprotected in good yield (71 %) using TBAF to give **215**.



Scheme 116

In an attempt to overcome the problems experienced in toluene, THF was instead used as the solvent. A range of metallocene catalysts were screened for the hydroalumination in both toluene and THF (**Scheme 117**), with the results shown in **Table 20**. As in the previous hydroalumination rate experiments, the conditions used were 1.5 eq HAICl₂·2THF and 5 mol% catalyst in refluxing solvent.



Scheme 117

Entry	Catalyst	Time (h)	Solvent	PhCCH (%) ^a	PhCH=CH ₂ (%) ^a	PhCH ₂ CH ₃ (%) ^a
1	Cp ₂ TiCl ₂	0.5	THF	32	66	2
2	Cp ₂ TiCl ₂	1.0	THF	28	70	2
3	Cp ₂ TiCl ₂	2.0	THF	23	75	2
4	Cp ₂ ZrCl ₂	0.17	Toluene	24	68	8
5	Cp ₂ ZrCl ₂	0.5	Toluene	21	70	9
6	Cp ₂ ZrCl ₂	1.0	Toluene	20	72	9
7	Cp ₂ ZrCl ₂	2.0	Toluene	16	74	10
8	Cp ₂ ZrCl ₂	8.0	Toluene	3	84	13
9	Cp ₂ ZrCl ₂	0.5	THF	29	69	2
10	Cp ₂ ZrCl ₂	1.0	THF	22	75	3
11	Cp ₂ ZrCl ₂	2.0	THF	19	77	4
12	Cp ₂ ZrHCl	0.17	Toluene	19	68	13
13	Cp ₂ ZrHCl	0.5	Toluene	17	73	10
14	Cp ₂ ZrHCl	1.0	Toluene	14	75	11
15	Cp ₂ ZrHCl	2.0	Toluene	10	76	14
16	Cp ₂ ZrHCl	8.0	Toluene	0	84	16
17	Cp ₂ ZrHCl	0.5	THF	21	76	4
18	Cp ₂ ZrHCl	1.0	THF	18	78	3
19	Cp ₂ ZrHCl	2.0	THF	16	79	4
20	Cp* ₂ ZrCl ₂	0.5	Toluene	35	62	3
21	Cp* ₂ ZrCl ₂	1.0	Toluene	35	62	2
22	Cp* ₂ ZrCl ₂	16.0	Toluene	33	65	2
23	Cp* ₂ ZrCl ₂	0.5	THF	46	53	1
24	Cp* ₂ ZrCl ₂	1.0	THF	41	58	1
25	Cp* ₂ ZrCl ₂	16.0	THF	24	75	1

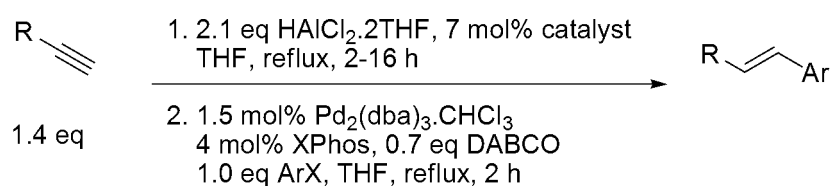
^a GC Yield.

Table 20

To achieve a similar yield of styrene to that in toluene, 2 h was required for Cp₂TiCl₂-catalysed hydroalumination (entry **3**). In general, the other catalyst/solvent combinations tested gave poorer selectivity for styrene over ethylbenzene, counteracting any increase in rate of reaction over Cp₂TiCl₂. However, as more bulky metallocene complexes provide greater selectivity, Cp*₂ZrCl₂ was also investigated. This proved useful in THF, as although requiring longer reaction time (16 h) to achieve a useful yield of vinylaluminium, this catalyst afforded the greatest selectivity for mono-hydroalumination (entry **25**).

Utilising these two catalyst systems in THF in combination with Pd-catalysed cross-coupling, a marked increase in yields was observed (**Scheme 118**, **Table 21**). (*E*)-Stilbene **210** was synthesised from bromobenzene in 94 % yield

with either catalyst (entries **4** and **7**). In the case of hydroalumination-cross-coupling of alkyl alkynes, those bearing linear groups also performed well with $\text{Cp}^*_2\text{ZrCl}_2$, although as branching was introduced and proximity to the triple bond increased (entries **1-3**), the yield of (*E*)-alkene product decreased, giving only 41 % of product **216** in the coupling of 3,3-dimethyl-1-butyne. Fortunately, this was resolved by the use of Cp_2TiCl_2 , giving 93 % yield of **216**.



Scheme 118

Entry	R	ArX	Catalyst	Yield (%) ^a
1	C ₆ H ₁₃	PhBr	$\text{Cp}^*_2\text{ZrCl}_2$	98
2	CH ₂ CH(CH ₃) ₂	PhBr	$\text{Cp}^*_2\text{ZrCl}_2$	88
3	^t Bu	PhBr	$\text{Cp}^*_2\text{ZrCl}_2$	41
4	Ph	PhBr	$\text{Cp}^*_2\text{ZrCl}_2$	94
5	Ph	3,5-Me ₂ C ₆ H ₃ Br	$\text{Cp}^*_2\text{ZrCl}_2$	55
6	^t Bu	PhBr	Cp_2TiCl_2	93
7	Ph	PhBr	Cp_2TiCl_2	94
8	Ph	PhI	$\text{Cp}^*_2\text{ZrCl}_2$	98
9	Ph	PhCl	$\text{Cp}^*_2\text{ZrCl}_2$	40
10	Ph	PhOTf	$\text{Cp}^*_2\text{ZrCl}_2$	86
11	Ph	PhOTf	Cp_2TiCl_2	26 ^b

^a Isolated Yield

^b 45 % yield of 1,1-diphenylethylene **217**.

Table 21

With coupling to aryl bromides successful, the methodology was then applied to iodo- and chlorobenzene, and phenyl triflate. Using $\text{Cp}^*_2\text{ZrCl}_2$ as the hydroalumination catalyst, the vinylaluminium generated from phenylacetylene coupled to iodobenzene and phenyl triflate to give excellent

yields of (*E*)-stilbene **210**. As could be expected given its lesser reactivity, chlorobenzene coupled in only 40 % yield (entry **9**). Coupling to phenyl triflate after hydroalumination with Cp_2TiCl_2 gave a mixture of **210** and the favoured 1,1-product **217**.

4.3.4 Molecular Modelling of Organoaluminium Species

Although experiments performed in Chapter 2 failed to isolate DABCO adducts of alkynylaluminium species, the favourability of these compounds to be formed *in situ* was of interest, as was that of the analogous vinylaluminium species proposed to be formed in our hydroalumination-cross-coupling reactions. To do this, molecular modelling was performed by the author using Spartan '06.¹³³

Initially, in order to assess the applicability of a low-level Hartree-Fock calculation to species with Al-N bonds such as the DABCO adducts involved in our cross-coupling reactions, the structures of trimethyl(quinuclidine)aluminium **218** and DABAL-Me₃ **219** (**Figure 2**) were modelled using the 3-21G basis set and the results compared with the crystal structures in the literature.^{134,135} Comparison of bond lengths and angles found good agreement for quinuclidine adduct **218** (**Table 22**), and although the results for DABAL-Me₃ **219** were in less good agreement, they were satisfactory (**Table 23**).

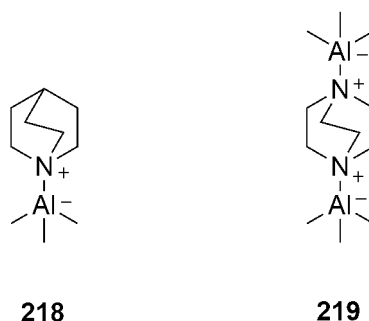


Figure 2

Bond Length (Å)	Crystal	HF 3-21G	Bond Angle (°)	Crystal	HF 3-21G
Al-N	2.06(1)	2.059	C-Al-C	114.3(3)	114.30
Al-C	2.02(1)	2.010	C-Al-N	104.5(3)	104.06
N-C	1.50(1)	1.505	C-N-Al	110.4(4)	109.72
CH ₂ -CH ₂	1.58(2)	1.556	C-N-C	108.6(5)	109.22
CH-CH ₂	1.50(2)	1.538	C-C-N	112.7(4)	110.73
			CH-CH ₂ -CH ₂	110.3(8)	109.11
			CH ₂ -CH-CH ₂	108.4(7)	108.81

Table 22

Bond Length (Å)	Crystal	HF 3-21G	Bond Angle (°)	Crystal	HF 3-21G
Al-N	2.065(8)	2.075	C-Al-C	114.3(3)	114.94
Al-C	1.954(11)	2.007	C-Al-N	104.0(4)	103.21
C-C	1.502(9)	1.554	C-N-C	107.2(5)	109.01
N-C	1.492(6)	1.500	N-C-C	111.5(6)	109.93
			C-N-Al	111.6(5)	109.30

Table 23

Whilst any errors inherent in the calculated values cannot be calculated, they are not significant, as the correspondence with literature values for these known structures, together with the use of a consistent method for all subsequent structures allowed the relative stability of species to be compared. This method was then used for subsequent calculations for other organoaluminium species.

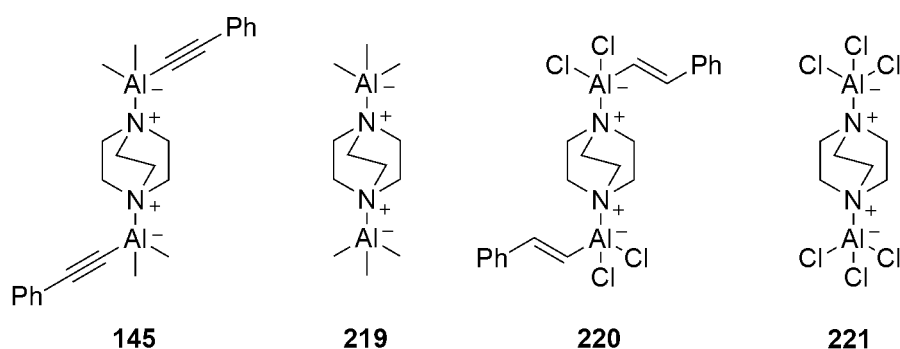


Figure 3

The bond dissociation energies for the Al-N bonds in alkynyl DABAL-Me₃ analogue **145** and vinylaluminium adduct **220**, as well as aluminium chloride

adduct **221** (**Figure 3**) were then calculated. This was accomplished by considering the adducts as EY_n , consisting of a monocoordinated DABCO adduct (Y) and the coordinating aluminium species (E), where $n = 1$ in all cases (as only one DABCO species is coordinated to the aluminium).¹³⁶ The average BDE (D_{bar}) for the Al-N bond could then be calculated using equation (1).

$$D_{\text{bar}}(E-Y) = [\Delta H^{\circ}_{\text{atom}}(EY_n)_{\text{calc}}]/n \quad (1)$$

where $\Delta H^{\circ}_{\text{atom}}(EY_n)_{\text{calc}}$ is the atomisation enthalpy calculated under standard conditions (298 K, 1 atm.) and is given by equation (2):

$$\Delta H^{\circ}_{\text{atom}}(EY_n)_{\text{calc}} = \{[U(E) + H(E)] + n[U(Y) + H(Y)]\} - [U(EY_n) + H(EY_n)] \quad (2)$$

U is the internal energy at 0 K (in Hartrees) and H is a correction to give the enthalpy under standard conditions. Full calculation details are given in Chapter 5. **Table 24** shows the calculated bond dissociation energies for the Al-N bond in each of the three species, in addition to that of DABAL-Me₃ **219**.

Al-N species	BDE (kcalmol ⁻¹)
145	-33.3692
220	-42.3859
221	-48.3601
219	-28.4092

Table 24

It can be seen that formation of all three is predicted to be favourable, given the negative energy change associated with their formation, with the AlCl₃ adduct **221** predicted to be the most stable. The Al-N bond in dimethyl(phenylethynyl)aluminium adduct **145** is predicted to be weaker than that in dichloroalane adduct **220**, perhaps due to the electron donating effect of the methyl groups decreasing the Lewis acidity of the alkynylaluminium. This

is borne out on comparison with DABAL-Me₃ **219**, where the Al-N bonding is slightly weaker again.

4.4 Conclusions

In examining various systems for the hydroalumination of alkenes and alkynes, many reactions were unsuccessful for a variety of reasons including selectivity issues and side reactions of organoaluminium reagents with, for example, the benzene solvent. However, novel use of HAlCl₂·2THF in Cp₂TiCl₂-catalysed hydroalumination of terminal acetylenes in toluene proceeded smoothly and the resulting vinylaluminium species were used in palladium-catalysed cross-coupling reactions with aryl bromides, giving moderate yields.

On switching to THF, cross-coupling was achieved with good to excellent yields of (*E*)-alkenes. This represents the first reported cross-coupling of vinylaluminium reagents derived from terminal aryl acetylenes, in addition to alkyl alkynes. Cp*₂ZrCl₂ has not previously been utilised as the catalyst in alkyne hydroalumination and provides greater selectivity than Cp analogues. Cp₂TiCl₂ is also effective, and provides greater yields of (*E*)-alkenes derived from alkynes with branching at the α-position. The methodology was also successfully applied to coupling with an aryl iodide, chloride and triflate. A paper on this work has been published.¹³⁷

Computational studies of organoaluminium reagents involved in our cross-coupling reactions have shown that Hartree-Fock calculations with the 3-21G basis set give reliable information when compared to published crystal structures. Calculation of bond dissociation energies for DABCO adducts of vinyl- and dimethylalkynylaluminium reagents have found that the formation of both species is predicted to be favourable, with the alkynylaluminium adduct predicted to be slightly less stable than that of the vinylaluminium.

4.5 Future Work

There are a number of ways in which the hydroalumination-cross-coupling of alkynes could be investigated further. The minimum catalyst loading required to give efficient reaction in both steps could be studied, as could the use of non-proprietary ligands such as A-^{ta}Phos **222** and Singer's ligand **223** (**Figure 4**) in place of XPhos, making the methodology potentially more attractive to industry.^{138,139} The vinylaluminium reagents could also be exploited in other reactions, such as addition to carbonyl compounds and conjugate addition reactions.

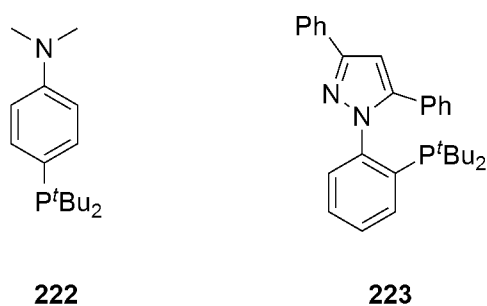


Figure 4

CHAPTER 5

Experimental Details

5.1 General

Solvents were dried prior to use: THF, Et₂O, 1,2-DME, 1,4-dioxane and toluene were freshly distilled from benzophenone ketyl; CH₂Cl₂ and CH₃CN were freshly distilled from CaH₂. Toluene was stored over 4 Å Molecular Sieves under argon. PE refers to the fraction of petroleum ether with a boiling range of 40-60 °C. All reactions involving air sensitive reagents were carried out under oxygen-free argon using oven-dried or flame-dried glassware. Flash column chromatography was carried out using Davisil silica gel 60 (0.035 - 0.070 mm particle size). Thin layer chromatography was carried out using Merck F₂₅₄ aluminium-backed silica plates.

Proton (400 MHz), carbon (100.6 MHz), fluorine (376.5 MHz) and phosphorus (162.0 MHz) NMR spectra were recorded on a Bruker DPX400, AV400 or AV(III)400 instrument. Chemical shifts are quoted as parts per million and referenced to CHCl₃ (7.27 ppm for ¹H, 77.0 ppm for ¹³C). Carbon and phosphorus NMR spectra were recorded with broadband proton decoupling. NMR spectra were assigned using DEPT, HMQC and COSY experiments. Infra-red spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer or Avatar 320 FT-IR fitted with a Nicolet Omni-Sampler ATR. Optical rotations were recorded at room temperature (20 °C) on a BS ADP 440 polarimeter (using the sodium D line; 259 nm) and [α]_D measurements are given in units of 10⁻¹ deg cm² g⁻¹ for concentration *c* in units of g/100 cm³. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. Mass spectrometry was carried out using either a Bruker MicroTOF or a Micromass AutoSpec instrument. Gas Chromatography was performed using either Varian GC3900 or GC430 apparatus.

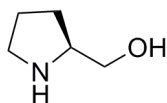
1,4-Diazabicyclo[2.2.2]octane (DABCO) was freshly sublimed before use. HAlCl₂.2THF was stored and weighed out in the glove box. Alkynes and aryl halides were dried with and stored over 4 Å molecular sieves. KO^tBu was purified by heating at 150-160 °C under vacuum for 1 h. All other commercially available compounds were used without further purification. For reactions involving trimethylsilyl cyanide, solvent and volatiles were removed

under high vacuum into a liquid nitrogen trap, and the trap was bleached to destroy any potential cyanide residues. Commercial lithium phenoxide (1 M in THF) was diluted to the required concentration prior to use.

5.2 Enamine *N*-oxide Synthesis and Reactivity

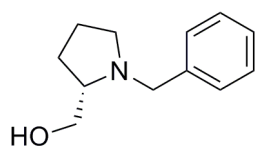
5.2.1 Mechanistic Study of Cyclic Enamine *N*-Oxide Formation

(*S*)-2-Pyrrolidinemethanol **25**



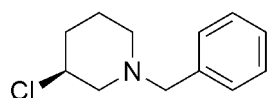
L-proline (10.0 g, 87.0 mmol, 1.00 eq) was slowly added to a stirred suspension of LiAlH_4 (6.61 g, 174 mmol, 2.00 eq) in THF (290 mL) at 2–5 °C under argon. The reaction was allowed to come to room temperature then heated at reflux under argon for 1 h, then stirred at room temperature for 16 h. The reaction mixture was cooled to –10 °C and H_2O (6.60 mL) was added very slowly (CARE exothermic), then 15% $\text{NaOH}_{(\text{aq})}$ solution (6.60 mL) and H_2O (19.8 mL) were added slowly, forming a white precipitate. The reaction mixture was filtered over Celite[®] and washed with EtOAc (3 x 10 mL). The solvent was removed *in vacuo* to yield aminoalcohol **25** (8.02 g, 91 %) as a red-brown oil, R_F (MeOH/ CH_2Cl_2 / Et_3N 5:93:2) 0.92; ^1H NMR (400 MHz, CDCl_3) δ : 3.60–3.45 (m, 1H, $\text{CH}_a\text{H}_b\text{OH}$), 3.38–3.25 (m, 2H, $\text{CH}_a\text{H}_b\text{OH}$ and NHCHCH_2OH), 3.02–2.81 (m, 2H, NHCH_2), 2.52–2.16 (br s, 2H, OH and NH), 1.92–1.60 (m, 3H, $\text{NHCH}_2\text{CH}_a\text{H}_b$ and $\text{NHCH}_2\text{CH}_2\text{CH}_2$), 1.50–1.34 (m, 1H, $\text{NHCH}_2\text{CH}_a\text{H}_b$); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 64.7 (CH_2OH), 46.4, 44.8 (NHCH and NHCH_2), 28.0, 27.6 (NHCH_2CH_2 and NHCHCH_2). Spectroscopic data consistent with those reported in the literature.¹⁴⁰

(S)-(1-Benzylpyrrolidin-2-yl)methanol 26



Aminoalcohol **25** (6.00 g, 59.3 mmol, 1.00 eq) was dissolved in MeCN (297 mL) and K_2CO_3 (8.20 g, 59.3 mmol, 1.00 eq) then BnBr (7.40 mL, 62.4 mmol, 1.05 eq) were added. The reaction mixture was stirred at 60 °C for 4 h, then allowed to cool to room temperature and stirred for 16 h. Ethyl acetate (300 mL) was added and the resulting solution was filtered over Celite[®]. The solvent was removed *in vacuo* to give the crude product. Purification by flash column chromatography (PE/EtOAc/Et₃N 2:1:0.05, 0.75 L) gave protected aminoalcohol **26** (6.52 g, 57 %) as a viscous orange-brown oil, *R_F* (PE/EtOAc/Et₃N 2:1:0.05) 0.18; ¹H NMR (400 MHz, CDCl₃) δ: 7.36-7.17 (m, 5H, Ph), 3.94 (d, 1H, *J* = 13.0 Hz, NCH_aH_bPh), 3.63 (dd, 1H, *J* = 10.7, 3.4 Hz, CH_aH_bOH), 3.39 (dd, 1H, *J* = 10.7, 2.0 Hz, CH_aH_bOH), 3.30 (d, 1H, *J* = 13.0 Hz, NCH_aH_bPh), 3.15 (br s, 1H, OH), 3.00-2.89 (m, 1H, NCH_aH_bCH₂), 2.76-2.65 (m, 1H, NCH), 2.33-2.20 (m, 1H, NCH_aH_bCH₂), 1.99-1.57 (m, 4H, NCH₂CH₂ and NCH₂CH₂CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ: 139.3 (Ph), 128.7 (Ph), 128.3 (Ph), 127.0 (Ph), 64.3 (CH₂OH), 61.7, 58.5, (NCH₂CH₂ and NCHCH₂), 54.4 (NCH₂Ph), 27.8, 23.5, (NCH₂CH₂ and NCH₂CH₂CH₂). Spectroscopic data consistent with those reported in the literature.¹⁴¹

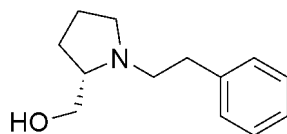
(S)-1-Benzyl-3-chloropiperidine 28



Benzylated aminoalcohol **26** (5.97 g, 31.2 mmol, 1.00 eq) and Et₃N (13.1 mL, 94.3 mmol, 3.00 eq) were dissolved in distilled CH₂Cl₂ (78.0 mL) under argon with stirring. The solution was cooled to 0 °C and MsCl (4.75 mL, 62.7 mmol, 2.00 eq) was added. The reaction was then allowed to warm to room temperature and stirred for 16 h. The reaction mixture was diluted with EtOAc (940 mL), washed with brine (4 x 40 mL) and the aqueous washings extracted with EtOAc (50 mL). The combined organic extracts were dried (Na₂SO₄) and the solvent was removed *in vacuo*. Purification by flash column

chromatography (PE/EtOAc/Et₃N 10:1:0.25, 0.6 L) and drying under vacuum for 1 h yielded chloroamine **28** (4.02 g, 61 %) as a yellow oil, *R_F* (PE/EtOAc/Et₃N 10:1:0.05) 0.38; ¹H NMR (400 MHz, CDCl₃) δ: 7.38-7.21 (m, 5H, Ph), 4.07-3.94 (m, 1 H, CHCl), 3.55 (s, 2H, NCH₂Ph), 3.13-2.99 (m, 1H, NCH_aH_bCHCl), 2.78-2.66 (m, 1H, NCH_aH_bCHCl), 2.29-2.03 (m, 3H, NCH₂CH₂ and CH₂CH_aH_bCHCl), 1.87-1.74 (m, 1H, CH₂CH_aH_bCHCl), 1.71-1.47 (m, 2H, NCH₂CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ: 137.9 (Ph), 129.0 (Ph), 128.2 (Ph), 127.1 (Ph), 62.7 (CHCl), 61.3 (NCH₂CHCl), 56.1, 52.8, (NCH₂Ph and NCH₂CH₂) 34.9 (CH₂CH₂CHCl), 24.8 (NCH₂CH₂). Spectroscopic data consistent with those reported in the literature.¹¹

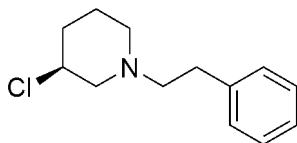
(S)-(1-Phenethylpyrrolidin-2-yl)methanol **27**



Aminoalcohol **25** (1.85 g, 18.3 mmol, 1.00 eq) was dissolved in MeCN (92.0 mL) and K₂CO₃ (2.53 g, 18.3 mmol, 1.00 eq) then (2-bromoethyl)benzene (2.65 mL, 19.2 mmol, 1.05 eq) were added. The reaction mixture was stirred at 60 °C for 4 h, then allowed to cool to room temperature and stirred for 16 h. Ethyl acetate (90.0 mL) was added and the resulting solution was filtered over Celite[®]. The solvent was removed *in vacuo* to give the crude product. Purification by flash column chromatography (PE/EtOAc/Et₃N 2:1:0.05, 0.75 L) gave protected aminoalcohol **27** (1.82 g, 48 %) as a yellow oil, *R_F* (PE/EtOAc/Et₃N 2:1:0.05) 0.19; IR (CHCl₃) 3442, 3066, 2951, 2876, 2809, 1603, 1497, 1454, 1405, 1242, 1120, 1081, 1023 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.35-7.26 (m, 2H, Ph), 7.25-7.18 (m, 3H, Ph), 3.56 (dd, 1H, *J* = 10.7, 3.6 Hz, CH_aH_bOH), 3.32 (dd, 1H, *J* = 10.7, 2.4 Hz, CH_aH_bOH), overlapped with 3.32-3.24 (m, 1H, NCHCH₂OH), 3.03-2.91 (m, 1H, NCH_aH_bCH₂CH₂), 2.89-2.69 (m, 2H, CH₂), 2.65-2.51 (m, 2H, CH₂), 2.41-2.30 (m, 1H, NCH_aH_bCH₂CH₂), 1.92-1.67 (m, 4H, NCH₂CH₂CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ: 140.4 (Ph), 128.6 (Ph), 128.4 (Ph), 126.1 (Ph), 64.5 (CH₂OH), 61.7, 55.9, (NCHCH₂OH and NCH₂CH₂Ph), 54.1 (NCH₂CH₂CH₂), 35.6 (CH₂Ph), 27.6, 23.7, (NCH₂CH₂CH₂); HRMS (ESI, pos.), *m/z* for

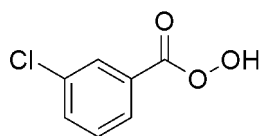
C₁₃H₁₉NO [(M + H)⁺], calcd. 206.1545, found 206.1538. Reported in the literature without spectroscopic data.¹⁴²

(S)-1-Phenethyl-3-chloropiperidine 29



Homobenzylated aminoalcohol **27** (1.49 g, 7.27 mmol, 1.00 eq) and Et₃N (3.05 mL, 21.9 mmol, 3.00 eq) were dissolved in distilled CH₂Cl₂ (19.0 mL) under argon with stirring. The solution was cooled to 0 °C and MsCl (1.10 mL, 14.6 mmol, 2.00 eq) was added. The reaction was then allowed to warm to room temperature and stirred for 16 h. The reaction mixture was diluted with EtOAc (220 mL), washed with brine (3 x 10 mL) and the aqueous washings extracted with EtOAc (10 mL). The combined organic extracts were dried (Na₂SO₄) and the solvent was removed *in vacuo*. Purification by flash column chromatography (PE/EtOAc/Et₃N 10:1:0.25, 0.7 L) yielded chloroamine **29** (1.15 g, 71 %) as a pale yellow oil, *R_F* (PE/EtOAc/Et₃N 10:1:0.25) 0.30; [*α*]_D -1.9 (*c* 0.98 in CHCl₃); **IR** (NaCl) 3384, 3027, 2947, 2804, 1602, 1497, 1453, 1373, 1352, 1276, 1158, 1098, 1032, 755, 699 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 7.34-7.25 (m, 2H, Ph), 7.25-7.16 (m, 3H, Ph), 4.10-3.96 (m, 1H, CHCl), 3.20-3.10 (m, 1H, NCH_aH_bCHCl), 2.88-2.74 (m, 3H, NCH_aH_bCHCl and NCH₂CH₂Ph), 2.68-2.58 (m, 2H, NCH₂CH₂CH₂), 2.37-2.25 (m, 1H, CH₂CH_aH_bCHCl), 2.23-2.10 (m, 2H, NCH₂CH₂Ph), 1.90-1.79 (m, 1H, CH₂CH_aH_bCHCl), 1.73-1.50 (m, 2H, NCH₂CH₂CH₂); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 140.2 (Ph), 128.7 (Ph), 128.4 (Ph), 126.0 (Ph), 61.4 (CHCl), 60.2 (NCH₂CHCl), 56.0 (NCH₂CH₂Ph), 52.9 (NCH₂CH₂CH₂), 34.8, 33.4, (NCH₂CH₂Ph and CH₂CH₂CHCl), 24.8 (NCH₂CH₂CH₂); **HRMS** (ESI, pos.), *m/z* for C₁₃H₁₈³⁵ClN [(M + H)⁺], calcd. 224.1206, found 224.1211.

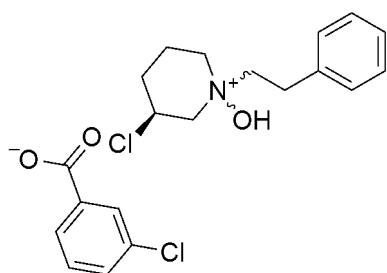
General Procedure 1: Drying of *m*CPBA



Using a procedure modified in the group from that used by Aggarwal,^{1,143} commercial *m*CPBA (75 %wt, 29.9 g) was dissolved in CH₂Cl₂ (350 mL) and washed with pH 7 buffer solution (3 x 150 mL). The organic layer was dried (Na₂SO₄) and carefully evaporated under reduced pressure to give *ca.* 21 g *m*CPBA. The purity was then determined by iodometric titration to be 95 %wt.¹⁴⁴

(3*S*)-3-Chloro-1-phenethylpiperidine *N*-oxide (as 3-chlorobenzoic acid salt)

30



A solution of chloroamine **29** (98.0 mg, 437 μ mol, 1.00 eq) in CH₂Cl₂ (2.00 mL) was added *via* syringe to a solution of *m*CPBA (125 mg, 727 μ mol, 75 %wt, 1.20 eq) in CH₂Cl₂ (4.00 mL), cooled with an ice-brine bath. The reaction mixture was stirred for 1 h, then an additional portion of *m*CPBA (20.5 mg, 119 μ mol, 75 %wt, 20.0 mol%) was added and the reaction stirred for a further 1 h to bring the reaction to completion. The solvent was removed under reduced pressure and the residue dried under vacuum for 16 h to give *N*-oxide 3-chlorobenzoic acid salt **30** (204 mg, 100 %, *ca.* 0.4 eq excess *m*CBA) as a very viscous pale yellow oil, $[\alpha]_D -3.7$ (*c* 1.04 in CHCl₃); **IR** (NaCl) 3012, 1713, 1575, 1432, 1240, 1073, 904 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ : 8.09 (t, 1H, *J* = 1.8 Hz, benzoate), 7.98 (dt, 1H, *J* = 7.8, 1.2 Hz, benzoate), 7.54 (ddd, 1H, *J* = 8.0, 2.2, 1.2 Hz, benzoate), 7.39 (t, 1H, *J* = 7.8 Hz, benzoate), 7.33-7.20 (m, 5H, Ph), 4.74-4.64 (m, 1H, CH_aH_bPh), 4.24-4.16 (m, 1H, NCH_aH_bCHCl), 4.14-4.07 (m, 1H, NCH_aH_bCHCl), 4.00-3.91 (m, 1H, CHCl), 3.87-3.76 (m, 1H, NCH_aH_bCH₂Ph), 3.42-3.33 (m, 1H, NCH_aH_bCH₂Ph), 3.32-

3.22 (m, 1H, $\text{CH}_a\text{H}_b\text{Ph}$), 3.12-3.00 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.66-2.50 (m, 1H, $\text{CH}_2\text{CH}_a\text{H}_b\text{CHCl}$), 2.48-2.39 (m, 1H, $\text{CH}_2\text{CH}_a\text{H}_b\text{CHCl}$), 1.94-1.86 (m, 1H, $\text{CH}_a\text{H}_b\text{CH}_2\text{CHCl}$), 1.72-1.60 (m, 1H, $\text{CH}_a\text{H}_b\text{CH}_2\text{CHCl}$); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 169.6 (Ph), 134.4 (Ph), 132.8 (Ph), 130.0 (Ph), 129.6 (Ph), 128.9 (Ph), 128.0 (Ph), 127.8 (Ph), 127.2 (Ph), 125.1 (Ph), 68.0 (NCH_2CHCl), 63.5 (CHCl), 60.7 ($\text{NCH}_2\text{CH}_2\text{Ph}$), 49.7 ($\text{NCH}_2\text{CH}_2\text{CH}_2$), 33.0 (PhCH_2), 28.8 ($\text{CH}_2\text{CH}_2\text{Cl}$), 20.0 ($\text{NCH}_2\text{CH}_2\text{CH}_2$); HRMS (ESI, pos.), m/z for $\text{C}_{12}\text{H}_{18}^{35}\text{ClNO}$ ($[\text{M} + \text{H}]^+$), calcd. 240.1150, found 240.1153. Stereochemistry at nitrogen could not be assigned.

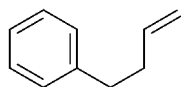
(3S)-3-Chloro-1-phenethylpiperidine N-oxide (as 3-chlorobenzoic acid salt)

30

A solution of chloroamine **29** (510 mg, 2.27 mmol, 1.00 eq) in distilled CH_2Cl_2 (2.00 mL) was added slowly *via* syringe to a solution of dried *m*CPBA (609 mg, 3.35 mmol, 95 %wt, 1.50 eq) in distilled CH_2Cl_2 (17.0 mL), cooled with an ice-brine bath. The reaction mixture was stirred for 19 h. The solvent was removed under reduced pressure and the residue dried under vacuum for 1 h to give *N*-oxide 3-chlorobenzoic acid salt **30** (962 mg, 100 %, *ca.* 1.3 eq excess *m*CBA) as a sticky yellow-brown crystalline solid. Data as above.

5.2.2 Synthesis of Acyclic Enamine N-Oxides

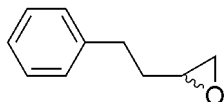
4-phenyl-1-butene 32



A dry 5 L round-bottomed flask fitted with a stirrer, condenser and dropping funnel, with argon inlet and outlet tubes fitted to the condenser, was charged with magnesium turnings (45.6 g, 1.87 mol, 3.60 eq) which had previously been washed with toluene (120 mL) then acetone (150 mL), then oven dried (3 h). Dry Et_2O (1250 mL) was added and the system was flushed with dry argon for 30 min, and a slow stream was maintained throughout the reaction. The magnesium turnings were stirred for 16 h before a small quantity (*ca.* 10 mg) of iodine and EtBr (1 mL) were added to initiate reaction. Once the iodine colour disappeared from the reaction mixture, the flask was cooled to

–10 °C in an ice-brine bath. A further portion of Et₂O (1000 mL) was added, followed by a solution of allyl chloride (132 g, 1.72 mol, 3.30 eq) in Et₂O (900 mL) added dropwise with rapid stirring over 4.5 h. Once addition was complete, the reaction mixture was stirred for a further 30 min at –10 °C. A solution of benzyl bromide (88.5 g, 520 mmol, 1.00 eq) in Et₂O (200 mL) was added dropwise then the reaction mixture was allowed to come room temperature and stirred under argon for 2.5 d. The reaction mixture was extracted in batches with H₂O (5 x 250 mL and 1 x 150 mL, slow addition of H₂O) then 1 M H₂SO_{4(aq)} (5 x 250 mL). The layers were separated and the organic layer evaporated under reduced pressure to give the crude product. Purification by distillation yielded the alkene **32** (18.7 g, 27 %) as a colourless oil, ¹H NMR (400 MHz, CDCl₃) δ: 7.40-7.29 (m, 2H, Ar), 7.29-7.19 (m, 3H, Ar), 5.99-5.87 (m, 1H, CH₂CH=CH₂), 5.16-5.00 (m, 2H, CH=CH₂), 2.78 (t, 2H, *J* = 7.6 Hz, PhCH₂), 2.45 (dt, 2H, *J* = 7.6, 7.6 Hz, PhCH₂CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ: 141.9 (Ph), 138.1 (CH=CH₂), 128.4 (Ph), 128.3 (Ph), 125.8 (Ph), 114.9 (=CH₂), 35.5 (CH₂), 35.4 (CH₂). Spectroscopic data consistent with those in the literature.¹⁴⁵

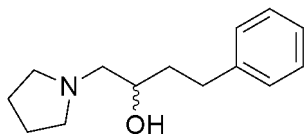
(±)-2-Phenethyloxirane **33**



Dried *m*CPBA (9.09 g, 52.7 mmol, 95 %wt, 1.25 eq) was added to a solution of 4-phenylbut-1-ene (5.28 g, 40.0 mmol, 1.00 eq) in CHCl₃ (200 mL) at 0 °C, and the reaction mixture was stirred for 30 min. The ice bath was removed and stirring was continued at room temperature for 21 h. The reaction mixture was then washed with a 1:1 mixture of H₂O and sat. NaHCO_{3(aq)} (2 x 50 mL) then pH 7 buffer (50 mL). The organic phase was dried (MgSO₄) and the solvent was removed *in vacuo* to give the crude product. Purification by flash column chromatography (PE/Et₂O 10:1, 0.7 L) gave epoxide **33** (5.38 g, 91 %) as a pale yellow oil, *R*_F (PE/Et₂O 10:1) 0.35; ¹H NMR (400 MHz, CDCl₃) δ: 7.35-7.28 (m, 2H, Ph), 7.26-7.19 (m, 3H, Ph), 3.00-2.94 (m, 1H, CH₂CHO), 2.90-2.72 (m, 3H, PhCH₂ and CH_aH_bO), 2.49 (dd, 1H, *J* = 5.0, 2.6 Hz, CH_aH_bO), 1.96-1.80 (m, 2H, PhCH₂CH₂); ¹³C NMR (100.6 MHz, CDCl₃)

δ : 141.2 (Ph), 128.4 (Ph), 128.3 (Ph), 126.0 (Ph), 51.7 (CHO), 47.2 (CH₂O), 34.2, 32.2, (PhCH₂ and PhCH₂CH₂). Spectroscopic data consistent with those reported in the literature.^{1,146}

(\pm)-4-phenyl-1-(pyrrolidin-1-yl)butan-2-ol **34**



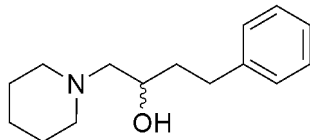
A heterogeneous mixture of epoxide **33** (5.38 g, 36.3 mmol, 1.00 eq) and pyrrolidine (3.60 mL, 43.6 mmol, 1.20 eq) in H₂O (19.0 mL) was stirred at room temperature for 23 h. The reaction mixture was diluted with EtOAc (35 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine (20 mL), filtered over SiO₂ and dried (MgSO₄). Concentration under reduced pressure yielded aminoalcohol **34** (3.27 g, 41 %) as a clear light amber oil of sufficient purity for use in the next step, *R_F* (PE/Et₂O/Et₃N 1:1:0.1) 0.33; ¹H NMR (400 MHz, CDCl₃) δ : 7.33-7.26 (m, 2H, Ph), 7.25-7.16 (m, 3H, Ph), 3.69 (dddd, 1H, *J* = 10.5, 7.6, 4.5, 3.0 Hz, CHOH), 2.85 (ddd, 1H, *J* = 13.9, 9.9, 6.0 Hz, PhCH_aH_b), 2.76-2.64 (m, 3H, PhCH_aH_b and NCH_aH_bCH₂), 2.62 (dd, 1H, *J* = 11.9, 10.5 Hz, NCH_aH_bCHOH), 2.51-2.41 (m, 2H, NCH_aH_bCH₂), 2.30 (dd, 1H, *J* = 11.9, 3.0 Hz, NCH_aH_bCHOH), 1.82-1.66 (m, 6H, PhCH₂CH₂ and NCH₂CH₂), OH signal not apparent; ¹³C NMR (100.6 MHz, CDCl₃) δ : 142.3 (Ph), 128.4 (Ph), 128.3 (Ph), 125.7 (Ph), 67.6 (CHOH), 61.9 (NCH₂CHOH), 54.0 (NCH₂CH₂), 36.8 (PhCH₂CH₂), 32.0 (PhCH₂), 23.6 (NCH₂CH₂). Spectroscopic data consistent with those reported in the literature.¹

(\pm)-4-phenyl-1-(pyrrolidin-1-yl)butan-2-ol **34**

A heterogeneous mixture of epoxide **33** (18.3 g, 123 mmol, 1.00 eq) and pyrrolidine (12.2 mL, 148 mmol, 1.20 eq) in H₂O (62.0 mL) was stirred at room temperature for 20 h. The reaction mixture was diluted with EtOAc (120 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (3 x 65 mL) and the combined organic extracts were washed with brine (65 mL), filtered over SiO₂ and dried (MgSO₄). Concentration under reduced

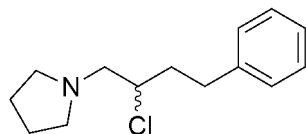
pressure yielded aminoalcohol **34** (25.6 g, 95 %) as an amber oil of sufficient purity for use in the next step. Data as above.

(±)-4-phenyl-1-(piperidin-1-yl)butan-2-ol 38



A heterogeneous mixture of epoxide **33** (4.53 g, 30.6 mmol, 1.00 eq) and piperidine (3.12 g, 36.7 mmol, 1.20 eq) in H₂O (15.0 mL) was stirred at room temperature for 20 h. The reaction mixture was diluted with EtOAc (35 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine (20 mL), filtered over SiO₂ and dried (MgSO₄). Concentration under reduced pressure yielded aminoalcohol **38** (5.89 g, 82 %) as a yellow-amber oil of sufficient purity for use in the next step, **IR** (NaCl) 3441, 2935, 1603, 1495, 1454, 1325, 1156, 1119, 1099, 1070, 1039, 877, 747, 699 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 7.32-7.26 (m, 2H, Ph), 7.25-7.16 (m, 3H, Ph), 3.73-3.65 (m, 1H, CHOH), 3.69 (br s, 1H, OH), 2.86 (ddd, 1H, *J* = 13.8, 9.9, 5.6 Hz, PhCH_aH_b), 2.71 (ddd, 1H, *J* = 13.8, 9.8, 6.7 Hz, PhCH_aH_b), 2.65-2.54 (m, 2H, NCH₂CH₂), 2.36-2.25 (m, 2H, NCH₂CH₂), 2.31 (dd, 1H, *J* = 12.3, 3.4 Hz, CH(OH)CH_aH_bN), 2.23 (dd, 1H, *J* = 12.3, 10.4 Hz, CH(OH)CH_aH_bN), 1.78-1.63 (m, 2H, PhCH₂CH₂), 1.63-1.50 (m, 4H, NCH₂CH₂), 1.49-1.41 (m, 2H, NCH₂CH₂CH₂); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 142.3 (Ph), 128.4 (Ph), 128.3 (Ph), 125.7 (Ph), 65.4 (CHOH), 64.7 (NCH₂CHOH), 54.6 (NCH₂CH₂), 36.8 (PhCH₂CH₂), 32.0 (PhCH₂), 26.1 (NCH₂CH₂), 24.3 (NCH₂CH₂CH₂); **HRMS** (ESI, pos.), *m/z* for C₁₅H₂₃NO ([M + H]⁺), calcd. 234.1858, found 234.1862. Reported in the literature without spectroscopic data.¹⁴⁷

(±)-1-(2-chloro-4-phenylbutyl)pyrrolidine 35



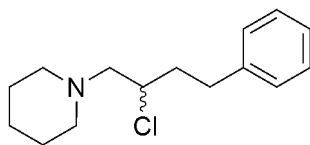
Neat SOCl₂ (1.60 mL, 22.4 mmol, 1.50 eq) was added dropwise to a solution of aminoalcohol **34** (3.23 g, 14.7 mmol, 1.00 eq) in distilled CH₂Cl₂ (35.0 mL)

at 0 °C under argon. When addition was complete, the ice bath was removed and the reaction mixture was refluxed under argon for 3 h. After cooling to room temperature, the reaction mixture was poured into a mixture of ice water (50 mL) and sat. NaHCO_{3(aq)} (50 mL). The aqueous phase was basified with 2 M NaOH_(aq), the layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were dried (MgSO₄) and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography (PE/Et₂O/Et₃N 10:1:0.2, 1.0 L) and drying under vacuum for 1 h gave chloroamine **35** (2.34 g, 67 %) as a pale amber oil, *R_F* (PE/Et₂O/Et₃N 10:1:0.2) 0.17; ¹H NMR (400 MHz, CDCl₃) δ: 7.33-7.27 (m, 2H, Ph), 7.25-7.18 (m, 3H, Ph), 3.93 (dddd, 1H, *J* = 9.6, 7.3, 6.4, 3.1 Hz, CHCl), 2.95 (ddd, 1H, *J* = 13.9, 9.4, 4.7 Hz, PhCH_aH_b), 2.80 (dd, 1H, *J* = 12.7, 7.3 Hz, NCH_aH_bCHCl), 2.77 (ddd, 1H, *J* = 13.9, 9.0, 7.3 Hz, PhCH_aH_b), 2.72 (dd, 1H, *J* = 12.7, 6.4 Hz, NCH_aH_bCHCl), 2.60-2.47 (m, 4H, NCH₂CH₂), 2.24 (dddd, 1H, *J* = 14.2, 9.4, 7.3, 3.1 Hz, CH₂CH_aH_bCHCl), 1.96 (dddd, 1H, *J* = 14.2, 9.6, 9.0, 4.7 Hz, CH₂CH_aH_bCHCl), 1.82-1.72 (m, 4H, NCH₂CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ: 141.2 (Ph), 128.5 (Ph), 128.4 (Ph), 126.0 (Ph), 63.4 (NCH₂CHCl), 60.6 (CHCl), 54.4 (NCH₂CH₂), 38.0 (PhCH₂CH₂), 32.4 (PHCH₂), 23.5 (NCH₂CH₂). Spectroscopic data consistent with those in the literature.¹

(±)-1-(2-chloro-4-phenylbutyl)pyrrolidine 35

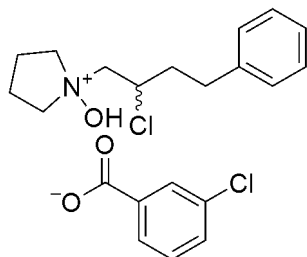
Neat SOCl₂ (12.7 mL, 175 mmol, 1.50 eq) was added dropwise to a solution of aminoalcohol **34** (25.6 g, 117 mmol, 1.00 eq) in distilled CH₂Cl₂ (250 mL) at 0 °C under argon. When addition was complete, the ice bath was removed and the reaction mixture was refluxed under argon for 3 h. After cooling to room temperature, the reaction mixture was poured into a mixture of ice water (390 mL) and sat. NaHCO_{3(aq)} (390 mL). The aqueous phase was basified with 2 M NaOH_(aq), the layers were separated, the organic phase was dried (MgSO₄) and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography (PE/Et₂O/Et₃N 10:1:0.2, 1.1 L) and drying under vacuum for 1 h gave chloroamine **35** (22.9 g, 83 %) as a yellow oil. Data as above.

(±)-1-(2-chloro-4-phenylbutyl)piperidine **39**



Neat SOCl_2 (2.70 mL, 36.8 mmol, 1.50 eq) was added dropwise to a solution of aminoalcohol **38** (5.73 g, 24.5 mmol, 1.00 eq) in distilled CH_2Cl_2 (58.0 mL) at 0 °C under argon. When addition was complete, the ice bath was removed and the reaction mixture was refluxed under argon for 3 h. After cooling to room temperature, the reaction mixture was poured into a mixture of ice water (50 mL) and sat. $\text{NaHCO}_{3(\text{aq})}$ (50 mL). The aqueous phase was basified with 2 M $\text{NaOH}_{(\text{aq})}$, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried (MgSO_4) and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography (PE/ Et_2O / Et_3N 10:1:0.2, 1.2 L) and drying under vacuum for 2 h gave chloroamine **39** (4.66 g, 75 %) as a yellow oil, R_F (PE/ Et_2O / Et_3N 10:1:0.2) 0.26; **IR** (NaCl) 3403, 3027, 2936, 2853, 1604, 1496, 1454, 1303, 1158, 1118, 1042, 748, 699 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ : 7.36-7.28 (m, 2H, Ph), 7.28-7.20 (m, 3H, Ph), 3.95 (dddd, 1H, $J = 9.6, 7.0, 6.4, 3.1$ Hz, CHCl), 2.93 (ddd, 1H, $J = 14.0, 9.4, 4.9$ Hz, PhCH_aH_b), 2.76 (ddd, 1H, $J = 14.0, 9.0, 7.0$ Hz, PhCH_aH_b), 2.65 (dd, 1H, $J = 12.6, 7.0$ Hz, $\text{NCH}_a\text{H}_b\text{CHCl}$), 2.53 (dd, 1H, $J = 12.6, 6.4$ Hz, $\text{NCH}_a\text{H}_b\text{CHCl}$), 2.40 (br s, 4H, NCH_2), 2.27 (dddd, 1H, $J = 14.2, 9.4, 7.0, 3.1$ Hz, $\text{PhCH}_2\text{CH}_a\text{H}_b$), 1.93 (dddd, 1H, $J = 14.2, 9.4, 9.0, 4.9$ Hz, $\text{PhCH}_2\text{CH}_a\text{H}_b$), 1.61-1.54 (m, 4H, NCH_2CH_2), 1.47-1.40 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$); **^{13}C NMR** (100.6 MHz, CDCl_3) δ : 141.3 (Ph), 128.5 (Ph), 128.4 (Ph), 126.0 (Ph), 65.9 (NCH_2CHCl), 59.4 (CHCl), 55.0 (NCH_2CH_2), 37.9 (PhCH_2CH_2), 32.4 (PhCH_2), 25.9 (NCH_2CH_2), 24.2 ($\text{NCH}_2\text{CH}_2\text{CH}_2$); **HRMS** (ESI, pos.), m/z for $\text{C}_{15}\text{H}_{22}^{35}\text{ClN}$ ($[\text{M} + \text{H}]^+$), calcd. 252.1519, found 252.1514.

(±)-1-(2-chloro-4-phenylbutyl)pyrrolidine N-oxide (as 3-chlorobenzoic acid salt) 36



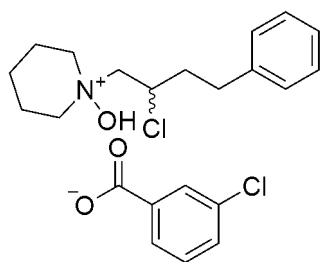
A solution of chloroamine **35** (2.34 g, 9.83 mmol, 1.00 eq) in distilled CH_2Cl_2 (4.00 mL) was added slowly *via* syringe to a solution of dried *m*CPBA (2.79 g, 16.2 mmol, 91 %wt, 1.50 eq) in distilled CH_2Cl_2 (81.0 mL) under argon, cooled with an ice-brine bath. The reaction mixture was allowed to come to room temperature and stirred for 23 h. The solvent was removed under reduced pressure and the residue dried under vacuum for 1 h to give *N*-oxide 3-chlorobenzoic acid salt **36** (5.42 g, 100 %, *ca.* 0.7 eq excess *m*CBA) as a brown oil, ^1H NMR (400 MHz, CDCl_3) δ : 8.06 (t, 1H, $J = 1.8$ Hz, benzoate), 7.95 (dt, 1H, $J = 7.8, 1.3$ Hz, benzoate), 7.53-7.47 (m, 1H, benzoate), 7.36 (t, 1H, $J = 7.8$ Hz, benzoate), 7.26-7.20 (m, 2H, Ph), 7.19-7.13 (m, 3H, Ph), 4.94-4.85 (m, 2H, CHCl and $\text{NCH}_a\text{H}_b\text{CHCl}$), 4.49-4.42 (m, 1H), 4.09-4.02 (m, 1H), ($\text{NCH}_a\text{H}_b\text{CH}_2$), 3.53 (dd, 1H, 14.0, 8.2 Hz, $\text{NCH}_a\text{H}_b\text{CHCl}$), 3.45-3.35 (m, 2H, $\text{NCH}_a\text{H}_b\text{CH}_2$), 2.94-2.76 (m, 2H, PhCH_2), 2.53-2.43 (m, 2H, PhCH_2CH_2), 2.29-2.19 (m, 1H), 2.17-2.03 (m, 3H), (NCH_2CH_2); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 169.7 (CO), 140.0 (Ar), 134.3 (Ar), 132.4 (Ar), 130.0 (Ar), 129.5 (Ar), 128.4 (Ar), 127.9 (Ar), 126.2 (Ar), 72.8 (NCH_2CHCl), 69.4, 67.0, (NCH_2CH_2), 54.9 (CHCl), 38.6 (PhCH_2), 31.9 (PhCH_2CH_2), 22.1, 20.4, (NCH_2CH_2). Spectroscopic data consistent with those in the literature.¹

(±)-1-(2-chloro-4-phenylbutyl)pyrrolidine N-oxide (as 3-chlorobenzoic acid salt) 36

A solution of chloroamine **35** (22.9 g, 96.4 mmol, 1.00 eq) in distilled CH_2Cl_2 (20.0 mL) was added slowly *via* syringe to a solution of dried *m*CPBA (26.3 g, 145 mmol, 94 %wt, 1.50 eq) in distilled CH_2Cl_2 (720 mL) under argon, cooled with an ice-brine bath. The reaction mixture was allowed to come to room temperature and stirred for 28 h. The solvent was removed under reduced

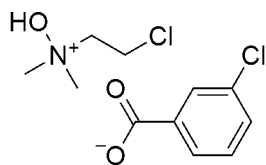
pressure and the residue dried under vacuum for 1 h to give *N*-oxide 3-chlorobenzoic acid salt **36** (44.1 g, 65 %, *ca.* 1.9 eq excess *m*CBA) as a waxy pale yellow solid. Data as above.

(±)-1-(2-chloro-4-phenylbutyl)piperidine *N*-oxide (as 3-chlorobenzoic acid salt) 40



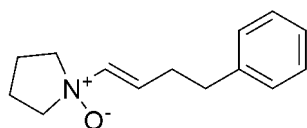
A solution of chloroamine **39** (1.85 g, 7.34 mmol, 1.00 eq) in distilled CH₂Cl₂ (4.00 mL) was added slowly *via* syringe to a solution of dried *m*CPBA (2.05 g, 11.1 mmol, 93 %wt, 1.50 eq) in distilled CH₂Cl₂ (55.0 mL) under argon, cooled with an ice-brine bath. The reaction mixture was allowed to come to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue dried under vacuum for 1 h to give *N*-oxide 3-chlorobenzoic acid salt **40** (3.71 g, 96 %, *ca.* 0.6 eq excess *m*CBA) as a yellow-orange oily solid, **IR** (CHCl₃) 3516, 2954, 2349, 1738, 1703, 1574, 1432, 1290, 1259, 1185, 1072, 905 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 8.07 (t, 1H, *J* = 1.7 Hz, benzoate), 7.97 (dt, 1H, *J* = 7.8, 1.4 Hz, benzoate), 7.50 (ddd, 1H, *J* = 7.9, 2.2, 1.0 Hz, benzoate), 7.36 (t, 1H, *J* = 8.9 Hz, benzoate), 7.32-7.12 (m, 5H, Ph), 4.84-4.76 (m, 1H, CHCl), 4.61 (d, 1H, *J* = 14.3 Hz, NCH_aH_bCHCl), 4.18-4.10 (m, 1H), 3.96-3.88 (m, 1H), (NCH_aH_bCH₂), 3.78 (dd, 1H, *J* = 14.3, 7.3 Hz, NCH_aH_bCH₂), 3.50-3.42 (m, 1H, NCH_aH_bCH₂), 3.35-3.25 (m, 1H, NCH_aH_bCHCl), 2.94-2.75 (m, 2H, PhCH₂), 2.34-2.18 (m, 3H), 2.17-2.06 (m, 1H), (NCH₂CH₂), 1.84-1.70 (m, 4H, NCH₂CH₂CH₂ and PhCH₂CH₂); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 169.7 (CO), 139.9 (Ar), 134.3 (Ar), 133.5 (Ar), 132.5 (Ar), 129.9 (Ar), 129.6 (Ar), 128.5 (Ar), 127.9 (Ar), 74.5 (NCH₂CHCl), 66.9, 63.7, (NCH₂CH₂), 53.8 (CHCl), 39.0 (PhCH₂), 31.8 (PhCH₂CH₂), 21.3, 20.9, (NCH₂CH₂), 20.7 (NCH₂CH₂CH₂); **HRMS** (ESI, pos.), *m/z* for C₁₅H₂₂³⁵ClNO ([M + H]⁺), calcd. 268.1468, found 268.1472.

N*-(2-chloroethyl)-dimethylamine *N*-oxide (as 3-chlorobenzoic acid salt) **42*



Commercial 2-dimethylaminoethyl chloride·HCl (498 mg, 3.46 mmol, 1.00 eq) was suspended in CH₂Cl₂ (10.0 mL) and NaOH (147 mg, 3.67 mmol, 1.00 eq) was added slowly. The mixture was stirred for 70 min until a clear solution was obtained. The solution was dried (MgSO₄) and filtered before commercial *m*CPBA (845 mg, 78 %wt, 3.82 mmol, 1.10 eq) was added at 0 °C under argon. The mixture was allowed to come to room temperature and stirred for 15.5 h. The solvent was removed under reduced pressure to give *N*-oxide 3-chlorobenzoic acid salt **42** (1.11 g, 100 %, *ca.* 0.25 eq excess *m*CBA) as a pale amber oil, ¹H NMR (400 MHz, CDCl₃) δ: 9.20 (br s, 1H, OH), 8.05 (t, 1 H, *J* = 1.8 Hz, benzoate), 7.94 (dt, 1H, *J* = 7.7, 1.3 Hz, benzoate), 7.50-7.47 (m, 1H, benzoate), 7.36 (t, 1H, *J* = 7.9 Hz, benzoate), 4.14 (t, 2H, *J* = 5.9 Hz, ClCH₂), 4.00 (t, 2H, *J* = 5.9 Hz, CH₂N), 3.57 (s, 6H, 2 x CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ: 169.4 (CO₂⁻), 134.2 (Ar), 132.1 (Ar), 129.9 (Ar), 129.4 (Ar), 127.8 (Ar), 70.8 (CH₂N(OH)Me₂), 58.2 (NMe₂), 36.2 (CH₂Cl). Spectroscopic data consistent with those reported in the literature.¹

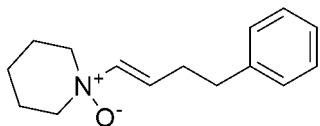
1-(4-phenylbut-1-enyl)pyrrolidine *N*-oxide **37**



A solution of *N*-oxide 3-chlorobenzoic acid salt **36** (5.42 g, 9.83 mmol, 1.00 eq) in THF (50.0 mL, 0.197 M) was added dropwise *via* syringe to a suspension of purified KO^{*t*}Bu (3.33 g, 29.7 mmol, 3.00 eq) in THF (50.0 mL, 0.594 M) under argon, cooled with an ice-brine bath. The reaction mixture was allowed to come to room temperature and stirred for 7 h. The THF was removed under reduced pressure, and the resulting solid was triturated in CH₂Cl₂, filtered over Celite®, and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (CH₂Cl₂/MeOH 95:5-70:30, 0.7 L) gave a brown oil, which when coevaporated with CHCl₃, then toluene,

gave enamine *N*-oxide **37** (1.28 g, 60 %) as a yellow-orange crystalline solid, *R_F* (CH₂Cl₂/MeOH 4:1) 0.40; ¹H NMR (400 MHz, CDCl₃) δ: 7.31-7.24 (m, 2H, Ph), 7.21-7.14 (m, 3H, Ph), 6.52 (dt, 1H, *J* = 13.2, 7.3 Hz, CHCHN), 6.11 (dt, 1H, *J* = 13.2, 1.4 Hz, CHCHN), 3.50-3.39 (m, 2H, NCH₂CH₂), 3.35-3.26 (m, 2H, NCH₂CH₂), 2.77 (t, 2H, *J* = 7.6 Hz, PhCH₂), 2.57-2.49 (m, 2H, NCH₂CH₂), 2.45 (qd, 2H, *J* = 7.6, 1.4 Hz, PhCH₂CH₂), 2.05-1.93 (m, 4H, NCH₂CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ: 140.8 (Ph), 139.1 (CHCHN), 128.5 (Ph), 128.2 (Ph), 126.1 (Ph), 125.4 (CHCHN), 69.5 (NCH₂CH₂), 34.9 (PhCH₂), 30.5 (PhCH₂CH₂), 21.8 (NCH₂CH₂). Spectroscopic data consistent with those reported in the literature.¹

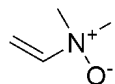
1-(4-phenylbut-1-enyl)piperidine *N*-oxide **41**



A solution of *N*-oxide 3-chlorobenzoic acid salt **40** (3.67 g, 7.00 mmol, 1.00 eq) in THF (35.0 mL, 0.200 M) was added dropwise *via* syringe to a suspension of purified KO^tBu (2.36 g, 21.0 mmol, 3.00 eq) in THF (35.0 mL, 0.601 M) under argon, cooled with an ice-brine bath. The reaction mixture was allowed to come to room temperature and stirred for 22 h. The THF was removed under reduced pressure, and the resulting solid was triturated in CH₂Cl₂, filtered over Celite[®], and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (CH₂Cl₂/MeOH 95:5-70:30, 0.9 L) gave an orange-brown oil, which when coevaporated with CHCl₃, then toluene, gave enamine *N*-oxide **41** (1.02 g, 63 %) as a pale yellow crystalline solid, *R_F* (CH₂Cl₂/MeOH 4:1) 0.76; IR (CHCl₃) 3621, 3463, 3009, 2976, 2895, 1391, 1247, 1046, 877 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.32-7.22 (m, 2H, Ph), 7.22-7.12 (m, 3H, Ph), 6.47 (dt, 1H, *J* = 13.3, 7.3 Hz, CHCHN), 6.03 (d, 1H, *J* = 13.3 Hz, CHCHN), 3.32-3.13 (m, 4H, NCH₂CH₂), 2.74 (t, 2H, *J* = 7.5 Hz, PhCH₂), 2.42 (td, 2H, *J* = 7.5, 7.3 Hz, PhCH₂CH₂), 2.38-2.26 (m, 2H, NCH₂CH_aH_b), 1.75-1.66 (m, 1H, NCH₂CH₂CH_aH_b), 1.61-1.54 (m, 2H, NCH₂CH_aH_b), 1.42-1.30 (m, 1H, NCH₂CH₂CH_aH_b); ¹³C NMR (100.6 MHz, CDCl₃) δ: 140.7 (Ph), 128.5 (Ph), 128.4 (Ph), 126.1 (Ph), 125.1 (CHCHN), 66.9 (NCH₂CH₂), 34.9 (PhCH₂), 30.5 (PhCH₂CH₂), 21.8 (NCH₂CH₂), 21.0

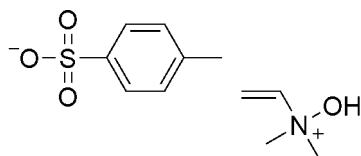
(NCH₂CH₂CH₂); **HRMS** (ESI, pos.), *m/z* for C₁₅H₂₁NO ([M + H]⁺), calcd. 232.1701, found 232.1700. Melting point not collected.

N,N-dimethylvinylamine *N*-oxide **6c**



A solution of *N*-oxide 3-chlorobenzoic acid salt **42** (11.2 g, 30.8 mmol, 1.00 eq) in THF (150 mL) was added dropwise to a suspension of KO^tBu (10.4 g, 92.5 mmol, 3.00 eq) in THF (150 mL) under argon and cooled with an ice-brine bath. The reaction mixture was allowed to come to room temperature and stirred for 15 h. The THF was removed under reduced pressure and the resulting solid was triturated with CH₂Cl₂ and filtered over a plug of Celite[®]. Evaporation under reduced pressure gave the crude product. This was filtered over a 20 mm plug of silica and washed with CH₂Cl₂ (4 x 15 mL), 1:1 CH₂Cl₂/MeOH (4 x 15 mL) and 1:3 CH₂Cl₂/MeOH (4 x 15 mL) into 3 separate Büchner flasks, and the solvent was removed under reduced pressure. The CH₂Cl₂/MeOH fractions were dried under high vacuum, and the CH₂Cl₂ fraction was purified by Kugelrohr distillation. The resulting products were combined to give enamine *N*-oxide **6c** (2.00 g, 74 %) as an amber oil, *R_F* (CH₂Cl₂/MeOH 4:1) 0.24; ¹H NMR (400 MHz, CDCl₃) δ: 6.47 (dd, 1H, *J* = 14.8, 7.7 Hz, H₂C=CHN), 5.89 (dd, 1H, *J* = 14.8, 2.2 Hz, NCH=CH_{trans}H_{cis}), 5.20 (dd, 1H, *J* = 7.7, 2.2 Hz, NCH=CH_{trans}H_{cis}), 3.31 (s, 6H, NMe₂); ¹³C NMR (100.6 MHz, CDCl₃) δ: 147.9 (CH₂=CHN), 107.6 (CH₂=CHN), 59.8 (NMe₂). Spectroscopic data consistent with those reported in the literature.¹

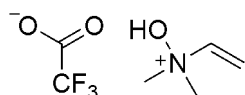
N,N-dimethylvinylamine *N*-oxide (as 4-toluenesulfonic acid salt) **43**



Crude enamine *N*-oxide **6c** (132 mg, 1.52 mmol, 1.00 eq) was dissolved in CDCl₃ (1.00 mL) under argon, and tosic acid monohydrate (287 mg, 1.52 mmol, 1.00 eq) was added. The reaction mixture was stirred for 30 min and the solvent was removed under reduced pressure to give salt **43** (338 mg,

86 %) as a peachy oil, ^1H NMR (400 MHz, CDCl_3) δ : 8.33 (br s, 1H, OH), 7.60 (d, 2H, $J = 8.2$ Hz, Ar), 7.05 (d, 2H, $J = 8.2$ Hz, Ar), 6.53 (dd, 1H, $J = 14.6, 7.9$ Hz, $\text{H}_2\text{C}=\text{CHN}$), 5.73 (dd, 1H, $J = 14.6, 3.5$ Hz, $\text{NCH}=\text{CH}_{\text{trans}}\text{H}_{\text{cis}}$), 5.25 (dd, 1H, $J = 7.9, 3.5$ Hz, $\text{NCH}=\text{CH}_{\text{trans}}\text{H}_{\text{cis}}$), 3.43 (s, 6H, NMe_2), 1.12 (s, 3H, Me); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 142.5 ($\text{CH}_2=\text{CHN}$), 140.6 (d, Ar), 128.9 (Ar), 125.5 (Ar), 112.2 ($\text{CH}_2=\text{CHN}$), 57.3 (NMe_2), 21.0 (Me).

N,N*-dimethylvinylamine *N*-oxide (as trifluoroacetic acid salt) **44*

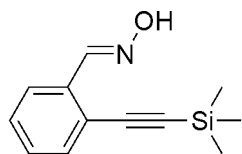


Crude enamine *N*-oxide **6c** (141 mg, 1.62 mmol, 1.00 eq) was dissolved in CDCl_3 (1.00 mL) under argon, and trifluoroacetic acid (120 μL , 1.62 mmol, 1.00 eq) was added. The reaction mixture was stirred for 30 min and the solvent was removed under reduced pressure to give salt **44** (385 mg, yield not determined due to unknown amount of trifluoroacetic acid relative to enamine *N*-oxide) as a pale orange oil, ^1H NMR (400 MHz, CDCl_3) δ : 9.00 (br s, OH), 6.58 (dd, 1H, $J = 14.6, 7.9$ Hz, $\text{H}_2\text{C}=\text{CHN}$), 6.03 (dd, 1H, $J = 14.6, 3.8$ Hz, $\text{NCH}=\text{CH}_{\text{trans}}\text{H}_{\text{cis}}$), 5.58 (dd, 1H, $J = 7.9, 3.8$ Hz, $\text{NCH}=\text{CH}_{\text{trans}}\text{H}_{\text{cis}}$), 3.67 (s, 6H, NMe_2); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 190.8 (CO), 143.0 ($\text{CH}_2=\text{CHN}$), 112.7 ($\text{CH}_2=\text{CHN}$), 57.8 (NMe_2), CF_3 not observed.

5.2.3 Potential Synthetic Routes to Enamine *N*-Oxides

5.2.3.1 Bromine-Activated Reaction of Alkynes with Hydroxylamines

(*E*)-2-(((trimethylsilyl)ethynyl)benzaldehyde oxime **46**

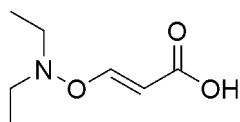


A solution of 2-[(trimethylsilyl)ethynyl]benzaldehyde (610 mg, 3.01 mmol, 1.00 eq), hydroxylamine hydrochloride (420 mg, 5.98 mmol, 2.00 eq) and pyridine (480 mg, 6.10 mmol, 2.00 eq) in EtOH (15.0 mL) was stirred at reflux for 2 h. The solvent was evaporated under reduced pressure and the residue

was quenched with H₂O (10 mL), extracted with EtOAc (2 x 30 mL) and dried (Na₂SO₄). The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (CH₂Cl₂/PE 1:1, 1.0 L) gave oxime **46** (560 mg, 86 %) as a white crystalline powder, *R_F* (CH₂Cl₂/PE 1:1) 0.31; ¹H NMR (400 MHz, CDCl₃) δ: 8.66 (s, 1H, CHN), 7.85-7.81 (m, 1H, Ar), 7.52-7.48 (m, 1H, Ar), 7.35-7.30 (m, 2H, Ar), 0.29 (s, 9H, Me); ¹³C NMR (100.6 MHz, CDCl₃) δ: 149.0 (C=N), 133.2 (Ar), 132.9 (Ar), 129.6 (Ar), 128.8 (Ar), 125.0 (Ar), 123.0 (Ar), 101.6 (ArC of alkyne), 100.6 (SiC of alkyne), -0.1 (SiMe₃). Spectroscopic data consistent with those in the literature.¹⁴⁸

5.2.3.2 Reaction of Hydroxylamines with Electron-deficient Alkynes

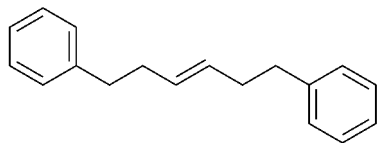
(*E*)-3-(diethylaminoxy)acrylic acid **48**



N,N-diethylhydroxylamine (361 mg, 4.05 mmol, 1.00 eq) was added dropwise to a solution of propiolic acid (280 mg, 3.99 mmol, 1.00 eq) in acetic acid (5.00 mL) and the reaction mixture was stirred for 1 h. Monitoring the reaction by NMR spectroscopy showed full consumption of the propiolic acid to (*E*)-3-(diethylaminoxy)acrylic acid **48** after 5 min; ¹H NMR (400 MHz, CDCl₃) δ: 9.56 (br s, OH), 7.79 (d, 1H, *J* = 12.6 Hz, *CHON*), 5.50 (d, 1H, *J* = 12.6 Hz, *CHCO₂H*), 2.87 (q, 4H, *J* = 7.2 Hz, 2 x NCH₂), 1.12 (t, 6H, *J* = 7.2 Hz, 2 x CH₃). Alkene geometry assigned by comparison of chemical shift and coupling constants with those for the corresponding (*E*)-methyl ester previously synthesised in the Woodward group.¹⁵

5.2.3.3 Development of Cross Metathesis Methodology

(*E*)-1,6-diphenylhex-3-ene **52**



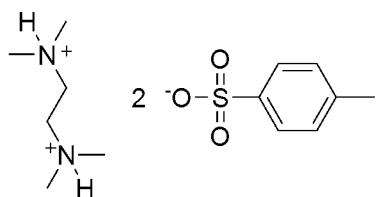
4-phenyl-1-butene (52.0 mg, 393 μmol , 1.00 eq) was dissolved in CDCl_3 (4.00 mL) under argon and Grubbs catalyst (1st Generation) (15.7 mg, 19.0 μmol , 5.00 mol%) was added. The reaction mixture was stirred for 21.5 h. A second portion of Grubbs I (15.2 mg, 18.0 μmol , 5.00 mol%) was added and the reaction mixture was stirred for a further 5 d. The reaction mixture was redissolved in CDCl_3 (2.00 mL) and a third portion of Grubbs I (15.2 mg, 18.0 μmol , 5.00 mol%) was added. The reaction mixture was stirred for 3 h, after which time NMR spectroscopy showed complete consumption of starting material. The solvent was removed under high vacuum to give a brown residue containing **52**; ^1H NMR (400 MHz, CDCl_3) δ : 7.38-7.12 (m, 10H, Ar), 5.51-5.47 (m, 2H, vinylic), 2.69-2.62 (m, 4H, CH_2), 2.34-2.27 (m, 4H, CH_2).

(*E*)-1,6-diphenylhex-3-ene **52**

4-phenyl-1-butene (47.4 mg, 359 μmol , 1.00 eq) was dissolved in CDCl_3 (2.00 mL) under argon and Grubbs catalyst (2nd Generation) (15.5 mg, 18.3 μmol , 5.00 mol%) was added. The reaction mixture was stirred for 25 h. NMR spectroscopy showed catalyst deactivation after 18 h, allowing 83 % conversion to product **52**.

(*E*)- N^1,N^1,N^2,N^2 -tetramethylethene-1,2-diaminium

4-methylbenzenesulfonate **53**



Enamine *N*-oxide **6c** (46.8 mg, 537 μmol , 1.00 eq) was dissolved in CDCl_3 (2.00 mL) under argon, dried *p*-TsOH (100 mg, 581 μmol , 1.08 eq) was added and the reaction mixture was stirred for 15 min. Grubbs catalyst (2nd

Generation) (24.1 mg, 28.3 μmol , 5.00 mol%) was added and the reaction mixture was stirred for 6 h. A slurry of 5 % Pd on charcoal (123 mg, 57.6 μmol , 10.0 mol%) in CDCl_3 (1.00 mL) was added under a stream of argon, the Schlenk tube was evacuated and backfilled with H_2 , and the reaction mixture was stirred for 15 h. Proton NMR spectroscopy showed consumption of starting material and presence of **53**; ^1H NMR (400 MHz, CDCl_3) δ : 7.58 (d, 4H, J = 6.0 Hz, Ar), 6.93 (d, 4H, J = 7.0 Hz, Ar), 5.09 (br s, NH), 2.67 (d, 12H, J = 1.5 Hz, NCH_3), 2.09 (br s, PhCH_3).

(*E*)- N^1,N^1,N^2,N^2 -tetramethylethene-1,2-diaminium

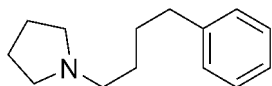
4-methylbenzenesulfonate **53**

Enamine *N*-oxide **6c** (49.7 mg, 570 μmol , 1.00 eq) was dissolved in CDCl_3 (2.00 mL) under argon, dried *p*-TsOH (103 mg, 598 μmol , 1.05 eq) was added and the reaction mixture was stirred for 15 min. Grubbs catalyst (2nd Generation) (2.3 mg, 2.71 μmol , 0.50 mol%) was added and the reaction mixture was stirred for 6 h. A slurry of 5 % Pd on charcoal (125 mg, 58.5 μmol , 10.0 mol%) in CDCl_3 (1.00 mL) was added under a stream of argon, the Schlenk tube was evacuated and backfilled with H_2 , and the reaction mixture was stirred for 15 h. Proton NMR spectroscopy showed consumption of starting material and presence of **53**.

5.2.4 Reactions of Enamine *N*-oxides

5.2.4.1 Reaction with Organoboron Reagents

General Procedure 2: Synthesis of 1-(4-phenylbutyl)pyrrolidine **54**



Catecholborane (85.0 μL , 797 μmol , 2.00 eq) was added to a stirred solution of enamine *N*-oxide **37** (86.4 mg, 398 μmol , 1.00 eq) in toluene (2.00 mL) under argon, and the reaction mixture was stirred at room temperature for 18 h. 4 M $\text{NaOH}_{(\text{aq})}$ (2 mL) was added at room temperature and the mixture stirred for 30 min. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with 4 M

NaOH_(aq) (3 x 5 mL), dried (Na₂SO₄) and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography (CH₂Cl₂/PE 1:1, 0.6 L) gave amine **54** (62.0 mg, 78 %) as a colourless oil, *R_F* (CH₂Cl₂/PE 1:1) 0.47; **IR** (NaCl) 3620, 3457, 3011, 2976, 2895, 1391, 1246, 1046, 877 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 7.32-7.25 (m, 2H, Ph), 7.22-7.15 (m, 3H, Ph), 3.23-3.14 (m, 2H, NCH₂ in chain), 2.80-2.72 (m, 2H, PhCH₂), 2.72-2.62 (m, 4H, NCH₂ in ring), 2.23-2.10 (m, 2H, PhCH₂CH₂ or PhCH₂CH₂CH₂), 1.92-1.80 (m, 4H, NCH₂CH₂ in ring), 1.64-1.54 (m, 2H, PhCH₂CH₂ or PhCH₂CH₂CH₂); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 141.9 (Ph), 128.4 (Ph), 128.3 (Ph), 125.9 (Ph), 63.9 (CH₂), 61.3 (CH₂), 35.6 (CH₂), 29.4 (CH₂), 24.9 (CH₂), 22.8 (CH₂); **HRMS** (EI, pos.), *m/z* for C₁₄H₂₁N (M⁺), calcd. 203.1674, found 203.1671. For full details of experimental conditions see **Table 25**.

Entry	Volume CatBH (μL)	μmol CatBH	eq CatBH	Mass 37 (mg)	μmol 37	Solvent	T (°C)	Time (h)	Work -up	Yield (%)
1	90.0	844	2.00	84.2	387	Toluene	70	19	A	0
2	45.0	422	1.00	90.6	417	Toluene	70	0.167	B	13
3	45.0	422	1.00	88.7	408	Toluene	70	0.167	C	8
4	85.0	797	2.00	87.5	403	Toluene	70	18	C	8
5	42.0	394	1.00	88.6	408	Toluene	rt	18	B	38
6	42.0	394	1.00	86.7	399	DMF	rt	18	B	12 ¹
7	42.0	394	1.00	85.6	394	DMF	rt	18	B	33 ^{1,2}
8	85.0	797	2.00	86.4	398	Toluene	rt	18	B	78
9	35.0	328	2.00	33.5	154	Toluene	-40 to rt	24	B	40

Work-up: A = 2 M NaOH, B = 4 M NaOH, C = 30 % H₂O₂.

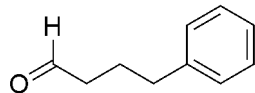
¹Yield figures inclusive of residual DMF.

²Reverse addition of enamine *N*-oxide **37** to catecholborane.

Table 25

5.2.4.2 Amine Synthesis by an Alternative Route for Structural Comparison

4-Phenylbutanal **56**



A three-neck 250 mL round-bottom flask containing a stirred solution of oxalyl chloride (1.00 mL, 11.7 mmol, 1.10 eq) in CH_2Cl_2 (25.0 mL) was equipped with a CaSO_4 drying tube and two pressure equalising dropping funnels, one containing a solution of DMSO (1.70 mL, 23.9 mmol, 2.20 eq) in CH_2Cl_2 (5.00 mL), the other containing a solution of 4-phenyl-1-butanol (1.51 g, 10.1 mmol, 1.00 eq) in CH_2Cl_2 (10.0 mL). The reaction mixture was cooled to $-50\text{ }^\circ\text{C}$, and the DMSO solution added. The reaction was allowed to stir for 2 min before adding the alcohol solution within 5 min. The reaction was stirred for 15 min before adding Et_3N (7.00 mL, 50.2 mmol, 5.00 eq) and stirring for a further 5 min. The reaction mixture was then allowed to warm to room temperature, H_2O (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The organic layers were combined, washed with brine (10 mL) and dried (MgSO_4). The solvent was removed *in vacuo* to give the crude product. The crude was then redissolved in CH_2Cl_2 (10 mL) and washed with 1 M $\text{HCl}_{(\text{aq})}$ (10 mL), water (10 mL), 5 % $\text{Na}_2\text{CO}_{3(\text{aq})}$ (10 mL) and water (10 mL). The organic phase was dried (MgSO_4) and the solvent was removed under reduced pressure to give aldehyde **56** (750 mg, 50%) as a pale yellow viscous oil, R_F (PE/EtOAc 10:1) 0.36; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 9.77 (t, 1H, $J = 1.6$ Hz, CHO), 7.33-7.28 (m, 2H, Ph), 7.24-7.10 (m, 3H, Ph), 2.68 (t, 2H, $J = 7.5$ Hz, PhCH_2), 2.47 (td, 2H, $J = 7.3, 1.6$ Hz, CH_2CHO), 1.98 (tt, 2H, $J = 7.5, 7.3$ Hz, PhCH_2CH_2); $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ : 202.3 (CHO), 141.2 (Ph), 128.4 (2C, Ph), 126.1 (Ph), 43.1 (CH_2), 35.0 (CH_2), 23.6 (CH_2). Spectroscopic data consistent with those in the literature.¹⁸

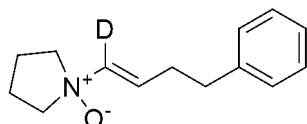
1-(4-phenylbutyl)pyrrolidine **54**

5 N Methanolic HCl (550 μL , 2.70 mmol, 2.00 eq) was carefully added to a solution of pyrrolidine (570 mg, 8.08 mmol, 6.00 eq) in MeOH (3.40 mL).

Aldehyde **56** (202 mg, 1.37 mmol, 1.00 eq) and NaBH₃CN (59.3 mg, 944 μmol, 70.0 mol%) were added and the resulting solution was stirred for 72 h. Concentrated HCl was added until pH <2, and the MeOH was removed *in vacuo*. The residue was taken up in H₂O (5 mL) and extracted with Et₂O (3 x 5 mL). The aqueous phase was basified with solid KOH until pH >10, saturated with NaCl and extracted with Et₂O (5 x 5 mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by column chromatography (CH₂Cl₂/PE 1:1, 0.3 L; CH₂Cl₂/MeOH 9:1, 0.5 L; 4:1, 0.2 L) gave amine **54** (158 mg, 57 %) as a colourless oil, **R_F** (CH₂Cl₂/MeOH 9:1) 0.28; **IR** (NaCl) 3620, 3458, 3011, 2977, 2895, 1391, 1247, 1046, 877 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 7.30-7.23 (m, 2H, Ph), 7.22-7.12 (m, 3H, Ph), 2.70-2.54 (m, 6H, PhCH₂ and NCH₂ in ring), 2.54-2.49 (m, 2H, NCH₂ in chain), 1.88-1.76 (m, 4H, NCH₂CH₂ in ring), 1.70-1.56 (m, 4H, PhCH₂CH₂ or PhCH₂CH₂CH₂); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 142.5 (Ph), 128.4 (Ph), 128.2 (Ph), 125.6 (Ph), 56.5 (CH₂), 54.3 (CH₂), 35.9 (CH₂), 29.5 (CH₂), 28.7 (CH₂), 23.4 (CH₂); **HRMS** (EI, pos.), *m/z* for C₁₄H₂₁N (M⁺), calcd. 203.1674, found 203.1669.

5.2.4.3 α-Deprotonation with Alkylolithium Bases

1-[(1-²H)4-phenylbut-1-enyl]pyrrolidine N-oxide **58**

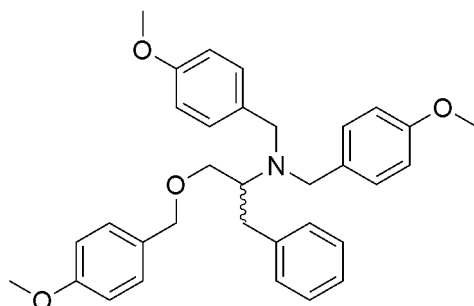


Enamine N-oxide **37** (197 mg, 908 μmol) was dissolved in THF (3.00 mL) under argon to give a standard solution of concentration 0.303 M, stored over 4 Å molecular sieves. A portion of this solution (1.00 mL, 303 μmol, 1.00 eq) was stirred and cooled to -50 °C under argon in a Schlenk tube. A solution of ^tBuLi in pentane (1.7 M, 260 μL, 442 μmol, 1.50 eq) was added and the reaction mixture was stirred for 5 min. D₂O (100 μL) was added and the solvent was removed under high vacuum. The residue was dissolved in CDCl₃ (600 μL), dried with 4 Å molecular sieves and filtered over cotton wool through a Pasteur pipette into an NMR tube. NMR spectroscopy showed complete conversion to product **58**, **¹H NMR** (400 MHz, CDCl₃) δ: 7.30-7.22

(m, 2H, Ph), 7.20-7.12 (m, 3H, Ph), 6.44 (t, $J = 6.9$ Hz, CH=CDN), 3.48-3.36 (m, 2H), 3.36-3.22 (m, 2H), (NCH₂), 2.74 (t, 2H, $J = 7.6$ Hz, PhCH₂), 2.54-2.45 (m, 2H, NCH₂CH₂), 2.41 (td, 2H, $J = 7.6, 6.9$ Hz, CH₂CH=CD), 2.00-1.86 (m, 2H, NCH₂CH₂), ¹³C NMR (100.6 MHz, CDCl₃) δ: 140.7 (Ph), 139.7 (CD), 128.4 (Ph), 128.3 (Ph), 126.0 (Ph), 124.8 (CHCD), 69.3 (NCH₂), 34.8 (PhCH₂), 30.3 (PhCH₂CH₂), 21.6 (NCH₂CH₂).

5.2.5 Investigations into the Owari Rearrangement

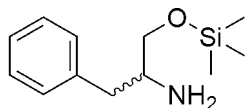
(±)-*N,N*-bis(4-methoxybenzyl)-1-(4-methoxybenzyloxy)-3-phenylpropan-2-amine **60**



4-Methoxybenzyl bromide (1.00 g, 5.00 mmol) and K₂CO₃ (3.45 g, 25.0 mmol) were added to a solution of (±)-2-amino-3-phenylpropan-1-ol **59** (380 mg, 2.50 mmol) in CH₃CN (30.0 mL). The heterogeneous mixture was heated to reflux and stirred for 24 h under argon. The reaction mixture was allowed to cool to room temperature and the solid K₂CO₃ was removed by filtration and washed with EtOAc (20 mL). The combined filtrates were concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (PE/EtOAc/Et₃N 6:1:0.05, 0.7 L) gave undesired tri-protected aminoalcohol (±)-**60** (421 mg, 33 %) as a pale yellow oil, *R*_F (PE/EtOAc/Et₃N 6:1:0.05) 0.30; IR (NaCl) 3050, 2838, 1612, 1512, 1465, 1301, 1247, 1173, 1103, 1036, 829 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.30-7.18 (m, 5H, Ar), 7.15-7.12 (m, 4H, Ar), 7.06-7.02 (m, 2H, Ar), 6.91-6.86 (m, 2H, Ar), 6.80-6.77 (m, 4H, Ar), 4.43-4.35 (m, 2H, ArCH₂O), 3.84-3.80 (m, 4H, ArCH₂N), 3.79 (s, 6H, OMe), 3.68 (s, 3H, OMe), 3.62-3.58 (m, 1H, NCHCH_aH_bO), 3.53-3.49 (m, 1H, NCHCH_aH_bO), 3.18-3.11 (m, 1H, NCHCH₂O), 2.92-2.78 (m, 2H, PhCH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ: 159.0 (Ar), 158.4 (Ar), 140.5 (Ar), 132.5 (Ar), 130.8 (Ar), 129.6 (Ar), 129.4 (Ar), 129.1 (Ar), 128.0 (Ar), 125.7 (Ar),

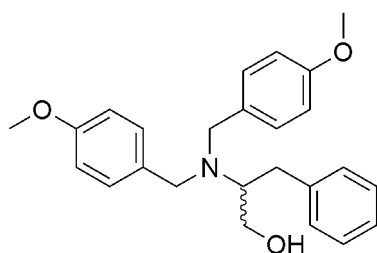
113.7 (Ph), 113.4 (Ph), 72.6 (OMe), 71.5 (OMe), 70.0 (ArCH₂O), 58.5 (ArCH₂N), 55.2 (CHCH₂O), 53.4 (BnCHN), 34.6 (PhCH₂); **HRMS** (ESI, pos.), *m/z* for C₃₃H₃₇NO₄ ([M + H]⁺), calcd. 512.2801, found 512.2776.

(±)-1-phenyl-3-(trimethylsilyloxy)propan-2-amine 61



Hexamethyldisilazane (1.35 mL, 6.25 mmol, 2.50 eq), Et₃N (5.00 mL) and 1,2-dichloroethane (10.0 mL) were added to (±)-2-amino-3-phenylpropan-1-ol **59** (380 mg, 2.50 mmol, 1.00 eq) and the reaction mixture was heated at reflux for 4 h. After allowing the reaction to cool to room temperature, the mixture was poured over sat. NaHCO_{3(aq)} (10 mL). The layers were separated, the aqueous phase was extracted with CH₂Cl₂ (3 x 5 mL) and the combined organic extracts were dried (MgSO₄). The solvent was removed *in vacuo* to give silyl ether **61** (710 mg, crude) as an oily pale yellow semi-solid, ¹H NMR (400 MHz, CDCl₃) δ: 7.33-7.27 (m, 2H, Ph), 7.25-7.20 (m, 3H, Ph), 3.64-3.57 (m, 1H, OCH_aH_b), 3.51-3.43 (m, 1H, OCH_aH_b), 3.14-3.08 (m, 2H, PhCH₂), 2.86-2.81 (m, 1H, CHNH₂), 0.13 (s, 9H, SiMe₃). Spectroscopic data consistent with those in the literature.¹⁴⁹

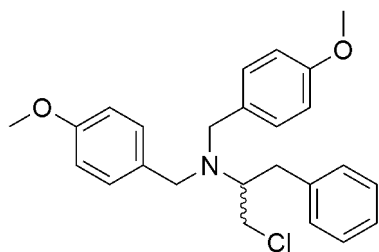
(±)-2-(bis(4-methoxybenzyl)amino)-3-phenylpropan-1-ol 62



4-Methoxybenzyl bromide (720 μL, 5.00 mmol, 2.00 eq) and K₂CO₃ (3.45 g, 25.0 mmol, 10.0 eq) were added to a solution of silyl ether **61** (710 mg crude, 2.50 mmol max., 1.00 eq) in CH₃CN (30.0 mL). The heterogeneous mixture was heated to reflux and stirred for 24 h. The reaction mixture was allowed to cool to room temperature and the solid K₂CO₃ was removed by filtration and washed with EtOAc (20 mL). The combined filtrates were concentrated under reduced pressure to give the crude product as a light brown oil. Cleavage of the

TMS group was found not to occur by washing with CsF_(aq), so the crude was redissolved in EtOAc (10 mL) and washed with 2 M HCl_(aq) (3 x 5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude *O*-deprotected aminoalcohol. Purification by flash column chromatography (solid load; PE/EtOAc/Et₃N 6:1:0.05, 0.7 L) and drying under high vacuum (6 h) gave *N*-protected aminoalcohol **62** (620 mg, 64 %) as a pale yellow oil, **R_F** (MeOH/Et₃N 1:0.02) 0.76; **IR** (NaCl) 3391, 2968, 2451, 1612, 1513, 1465, 1249, 1174, 1036, 832 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 7.32-7.24 (m, 4H, Ar), 7.22-7.15 (m, 4H, Ar), 7.12-7.08 (m, 1H, Ar), 6.90-6.82 (m, 4H, Ar), 4.63 (s, 1H, OH), 3.89-3.77 (m, 1H, NCHCH_aH_bOH), 3.80 (s, 6H, OMe), 3.53-3.37 (m, 1H, NCHCH_aH_bOH), 3.12-3.00 (m, 7H, NCH₂Ar, NCHCH₂OH, PhCH₂); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 131.1 (Ar), 130.1 (Ar), 128.9 (Ar), 128.5 (Ar), 126.2 (Ar), 113.9 (Ar), 55.2 (OMe), 52.3 (CH₂OH), 45.5 (ArCH₂N), 31.7 (NCHBn), 8.7 (PhCH₂); **HRMS** (ESI, pos.), *m/z* for C₂₅H₂₉NO₃ ([M + H]⁺), calcd. 392.2226, found 392.2220.

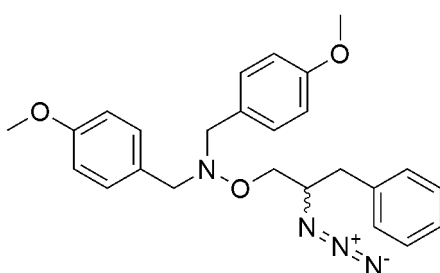
(±)-1-chloro-*N,N*-bis(4-methoxybenzyl)-3-phenylpropan-2-amine **63**



Methanesulfonyl chloride (130 μL, 1.72 mmol, 2.00 eq) was added to a stirred solution of aminoalcohol **62** (328 mg, 838 μmol, 1.00 eq) and Et₃N (350 μL, 2.52 mmol, 3.00 eq) in distilled CH₂Cl₂ (2.50 mL) at 0 °C under argon. The reaction mixture was then allowed to come to room temperature and stirred for 22 h. The reaction mixture was diluted with EtOAc (25 mL), washed with brine (3 x 10 mL) and dried (Na₂SO₄). The solvent was removed *in vacuo* to give the crude product as a pale amber oil. Purification by flash column chromatography (PE/EtOAc/Et₃N 10:1:0.25, 0.45 L) and equilibration in CHCl₃ (10 mL) at 50 °C for 24 h gave *N*-protected β-chloroamine **63** (45.0 mg, 13 %) as a pale amber oil, **R_F** (PE/EtOAc/Et₃N 10:1:0.25) 0.58; **¹H NMR** (400 MHz, CDCl₃) δ: 7.30-7.23 (m, 7H, Ar), 7.10-7.06 (m, 2H, Ar), 6.89-6.85 (m,

4H, Ar), 4.04-3.96 (m, 1H, NCHBn), 3.81 (s, 6H, OMe), 3.67-3.62 (m, 2H, CH₂Cl), 3.55-3.50 (m, 2H, NCH_aH_bAr), 3.30 (dd, 1H, *J* = 14.3, 4.1 Hz, PhCH_aH_b), 2.79 (d, 2H, *J* = 7.0 Hz, NCH_aH_bAr), 2.60 (dd, 1H, *J* = 14.3, 9.2 Hz, PhCH_aH_b); ¹³C NMR (100.6 MHz, CDCl₃) δ: 158.7 (Ar), 138.4 (Ar), 131.1 (Ar), 130.1 (Ar), 129.3 (Ar), 128.2 (Ar), 126.5 (Ar), 113.7 (Ar), 61.4 (CH₂Cl), 60.5 (OMe), 58.6 (ArCH₂N), 55.2 (NCHBn), 42.3 (PhCH₂). MS and IR data not collected.

(±)-O-(2-azido-3-phenylpropyl)-N,N-bis(4-methoxybenzyl)hydroxylamine
64

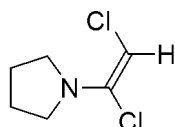


A solution of β-chloroamine **63** (44.8 mg, 109 μmol, 1.00 eq) in CH₂Cl₂ (3.00 mL) was added to a solution of *m*CPBA (30.8 mg, 178 μmol, 95 %wt, 1.55 eq) in CH₂Cl₂ (2.00 mL) at 0 °C, and the reaction mixture was stirred for 40 min. Tetrabutylammonium azide (110 mg, 387 μmol, 3.55 eq) and Et₃N (150 μL, 1.10 mmol, 10.0 eq) were added and the reaction mixture was stirred at 0 °C for 2.5 h. The solution was diluted with PE/Et₃N (50:1, 5 mL), filtered over silica gel, and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography (PE/EtOAc/Et₃N 2:1:0.05, 0.3 L; CH₂Cl₂/MeOH 9:1, 0.4 L) gave azide **64** (42.0 mg, 88 %, inseparable from *m*-chlorobenzoate) as a colourless oil, *R*_F (PE/EtOAc/Et₃N 2:1:0.05) 0.94; IR (CHCl₃) 3007, 2935, 2839, 2103, 1720, 1613, 1513, 1248, 1175, 1036 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.96 (m, 1H, benzoate), 7.86 (m, 1H, benzoate), 7.54 (m, 1H, benzoate), 7.38 (t, 1H, *J* = 7.9 Hz, benzoate), 7.30-7.13 (m, 9H, Ar), 7.02-6.97 (m, 2H, Ar), 6.85 (d, 2H, *J* = 8.5 Hz, Ar), 3.80 (s, 10H, OMe and NCH₂Ar), 3.55-3.47 (m, 1H, N₃CH), 3.05-3.00 (m, 1H, CHN₃CH_aH_bPh), 2.95-2.90 (m, 1H, CHN₃CH_aH_bPh), 2.75-2.70 (m, 1H, CHN₃CH_aH_bO), 2.49-2.43 (m, 1H, CHN₃CH_aH_bO); ¹³C NMR (100.6 MHz, CDCl₃) δ: 146.0 (CHN₃), 137.9 (Ar), 130.9 (Ar), 129.4 (Ar), 129.3 (Ar), 128.3

(Ar), 126.2 (Ar), 114.3 (Ar), 113.6 (Ar), 61.8 (OMe), 55.2 (OCH₂), 37.0 (ArCH₂N), 21.0 (PhCH₂); **HRMS** (ESI, pos.), *m/z* for C₂₅H₂₈N₄O₃ ([M + H]⁺), calcd. 433.2240, found 433.2212.

5.2.6 Synthesis of Ynamine and Ynamine *N*-oxide Precursors

1-(1,2-dichlorovinyl)pyrrolidine **69**

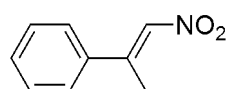


A mixture of tetrachloroethylene (2.00 mL, 19.6 mmol, 1.00 eq), dry pyrrolidine (1.60 mL, 19.6 mmol, 1.00 eq) and Cs₂CO₃ (6.38 g, 19.6 mmol, 1.00 eq) was stirred and heated at 120 °C under argon for 6 h. The reaction mixture was allowed to cool to room temperature and was filtered over Celite[®], washing the filter cake with Et₂O. The solvent was evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation yielded dichloroalkene **69** (169 mg, 5 %) as a viscous brown oil, **IR** (CHCl₃) 2982, 2885, 1670, 1649, 1434, 1342, 1242 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 6.13 (s, 1H, alkene-CH), 3.67 (t, 2H, *J* = 6.9 Hz, NCH₂), 3.56 (t, 2H, *J* = 7.0 Hz, NCH₂), 2.07-2.00 (m, 2H, NCH₂CH₂), 1.96-1.87 (m, 2H, NCH₂CH₂); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 161.8 (ClCN), 65.9 (CHCl), 47.3 (CH₂), 46.7 (CH₂), 26.3 (CH₂), 23.8 (CH₂); **HRMS** (EI) *m/z* for C₆H₉³⁵Cl₂N ([M + O]⁺), calcd. 181.0061, found 181.0056.

5.3 Asymmetric Conjugate Addition Reactions

5.3.1 Conjugate Addition of Alkyl- and Vinylaluminium Species to Nitroalkenes

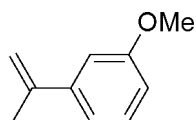
(*E*)-1-nitro-2-phenylpropene **71**



A solution of copper(II) tetrafluoroborate was prepared by dissolving CuO (321 mg, 4.03 mmol, 20.0 mol%) in 35 % HBF_{4(aq)} (1.60 mL, 8.04 mmol,

40.0 mol%). Acetonitrile (20.0 mL) and NaNO₂ (1.65 g, 23.9 mmol, 1.20 eq) were added and the mixture was stirred for 2 min. α -Methylstyrene (2.35 g, 19.9 mmol, 1.00 eq) and iodine (1.53 g, 6.04 mmol, 30.0 mol%) were added and the reaction mixture was stirred at room temperature for 7 h. H₂O (25 mL) was added and the precipitated copper(I) iodide was removed by filtration over Celite[®]. The filtrate was extracted with CH₂Cl₂ (3 x 25 mL), washed with 5 % Na₂S₂O_{3(aq)} (25 mL) and dried (Na₂SO₄). Evaporation under reduced pressure gave the crude product. Purification by flash column chromatography (hexane/Et₂O 9:1, 0.6 L) gave pure (*E*)-nitroalkene **71** (252 mg, 8 %) as a yellow oil, and a 10.5:1 mixture of (*E*)- and (*Z*)-isomers (1.63 g, 50 %) as a red-orange oil. (*E*)-**71**: *R*_F (hexane/Et₂O 9:1) 0.40; ¹H NMR (400 MHz, CDCl₃) δ : 7.48-7.44 (m, 5H, Ar), 7.32 (q, 1H, *J* = 1.5 Hz, CHNO₂), 2.66 (d, 3H, *J* = 1.5 Hz, CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ : 149.9 (PhC), 138.3 (Ar), 136.3 (CHNO₂), 130.3 (Ar), 129.0 (Ar), 126.8 (Ar), 18.6 (CH₃). (*Z*)-**71**: *R*_F (hexane/Et₂O 9:1) 0.20. Spectroscopic data consistent with those reported in the literature.³⁷

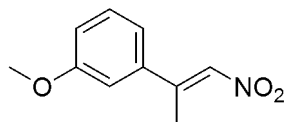
2-(3'-methoxyphenyl)propene **82**



A solution of ⁿBuLi (5.00 mL of a 1.6 M solution in hexane, 8.00 mmol, 1.00 eq) was added to a stirred suspension of methyltriphenylphosphonium bromide (2.86 g, 7.99 mmol, 1.00 eq) in dry Et₂O (25.0 mL) under argon. The mixture was stirred for 30 min then 3-methoxyacetophenone (1.20 g, 7.96 mmol, 1.00 eq) was added and stirring was continued for 24 h. The solution was poured onto H₂O (20 mL) and the layers were separated. The aqueous phase was extracted with Et₂O (3 x 20 mL) and the combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (hexane 0.3 L; hexane/Et₂O 19:1, 0.5 L) gave unreacted starting material (39 %) plus the desired methoxyphenyl propene **82** (473 mg, 40 %) as a pale yellow oil, *R*_F (hexane/Et₂O 19:1) 0.50; ¹H NMR (400 MHz, CDCl₃) δ : 7.30-7.24 (m, 1H, Ar), 7.11-7.07 (m, 1H, Ar), 7.04-7.01 (m, 1H, Ar), 6.86-6.82 (m, 1H, Ar),

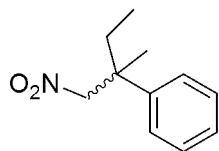
5.40-5.38 (m, 1H, $\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$), 5.12-5.10 (m, 1H, $\text{CH}_{\text{cis}}\text{H}_{\text{trans}}$), 3.85 (s, 3H, OMe), 2.17-2.16 (m, 3H, CH_3C); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 159.5 (Ar), 143.1 (PhC), 142.8 (Ar), 129.1 (Ar), 118.1 (Ar), 112.7 (Ar), 112.6 (Ar), 111.5 (CH_2), 55.2 (OCH_3), 21.9 (CH_3). Spectroscopic data consistent with those reported in the literature.³⁷

(*E*)-2-(3'-methoxyphenyl)-1-nitropropene 83



Solid 2-(3'-methoxyphenyl)propene **82** (153 mg, 1.04 mmol, 1.00 eq), NaNO_2 (692 mg, 10.0 mmol, 10.0 eq) and CAN (550 mg, 1.00 mmol, 1.00 eq) were suspended in CHCl_3 (100 mL) and acetic acid (700 μL , 12.1 mmol, 12.0 eq) was added. The mixture was sonicated for 1 h in a sealed flask connected to a bubbler. CHCl_3 (20 mL) was added and the solution was washed with sat. $\text{NaHCO}_{3(\text{aq})}$ (3 x 10 mL) and H_2O (3 x 10 mL) then dried (MgSO_4). The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (hexane/ Et_2O 9:1, 0.5 L) followed by drying under high vacuum (30 min) gave nitroalkene **83** (108 mg, 54 %) as a pale yellow oil, R_F (hexane/ Et_2O 9:1) 0.20; ^1H NMR (400 MHz, CDCl_3) δ : 7.38-7.33 (m, 1H, Ar), 7.32 (q, 1H, $J = 1.5$ Hz, CHNO_2), 7.05-7.03 (m, 1H, Ar), 7.01-6.98 (m, 1H, Ar), 6.97-6.95 (m, 1H, Ar), 3.86 (s, 3H, OCH_3), 2.64 (d, 3H, $J = 1.5$ Hz, CH_3C); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 159.9 (Ph), 149.8 (PhC), 139.7 (Ph), 136.4 (CHNO_2), 130.1 (Ph), 119.2 (Ph), 115.6 (Ph), 112.6 (Ph), 55.4 (OCH_3), 18.6 (CH_3). Spectroscopic data consistent with those reported in the literature.³⁷

(\pm)-1-nitro-2-methyl-2-phenylbutane 72



(*E/Z*)-nitroalkene **71** (301 mg, 1.84 mmol) was dissolved in dry Et_2O (6.00 mL) to give a 0.307 M standard solution. Copper acetate (1.8 mg, 9.9 μmol , 3.2 mol%) and $\text{P}(\text{OPh})_3$ (4.8 μL , 18 μmol , 5.9 mol%) were dissolved in

distilled Et₂O (2.00 mL) under argon and the reaction mixture was stirred for 20 min. A portion of nitroalkene standard solution (1.00 mL, 307 μmol, 1.00 eq) was added, followed by triethylaluminium (800 μL of a 1 M solution in heptane, 800 μmol, 2.61 eq) and the reaction mixture was stirred at room temperature for 23.5 h. Saturated NH₄Cl_(aq) (1 mL) was added dropwise, followed by 10 % HCl_(aq) (2 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 x 2 mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification and characterisation details are given below.

(±)-1-nitro-2-methyl-2-phenylbutane 72

Solid Cu(TC) (1.8 mg, 9.4 μmol, 3.1 mol%) and P(OPh)₃ (4.8 μL, 18 μmol, 5.9 mol%) were dissolved in distilled Et₂O (2.00 mL) under argon and the reaction mixture was stirred for 20 min. A portion of nitroalkene standard solution (1.00 mL, 307 μmol, 1.00 eq) was added, followed by triethylaluminium (800 μL of a 1 M solution in heptane, 800 μmol, 2.61 eq) and the reaction mixture was stirred at room temperature for 23.5 h. Saturated NH₄Cl_(aq) (1 mL) was added dropwise, followed by 10 % HCl_(aq) (2 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 x 2 mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification and characterisation details are given below.

(±)-1-nitro-2-methyl-2-phenylbutane 72

Copper acetate (1.8 mg, 9.9 μmol, 3.2 mol%) and PPh₃ (4.9 mg, 19 μmol, 6.2 mol%) were dissolved in distilled Et₂O (2.00 mL) under argon and the reaction mixture was stirred for 20 min. A portion of nitroalkene standard solution (1.00 mL, 307 μmol, 1.00 eq) was added, followed by triethylaluminium (800 μL of a 1 M solution in heptane, 800 μmol, 2.61 eq) and the reaction mixture was stirred at room temperature for 23.5 h. Saturated NH₄Cl_(aq) (1 mL) was added dropwise, followed by 10 % HCl_(aq) (2 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 x 2 mL). The combined organic extracts were dried (MgSO₄) and evaporated

under reduced pressure to give the crude product. Purification and characterisation details are given below.

(±)-1-nitro-2-methyl-2-phenylbutane 72

Solid Cu(TC) (1.8 mg, 9.4 μmol , 3.1 mol%) and PPh_3 (5.0 mg, 19 μmol , 6.2 mol%) were dissolved in distilled Et_2O (2.00 mL) under argon and the reaction mixture was stirred for 20 min. A portion of nitroalkene standard solution (1.00 mL, 307 μmol , 1.00 eq) was added, followed by triethylaluminium (800 μL of a 1 M solution in heptane, 800 μmol , 2.61 eq) and the reaction mixture was stirred at room temperature for 23.5 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (1 mL) was added dropwise, followed by 10 % $\text{HCl}_{(\text{aq})}$ (2 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 2 mL). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification and characterisation details are given below.

(±)-1-nitro-2-methyl-2-phenylbutane 72

Copper acetate (1.9 mg, 10 μmol , 3.3 mol%) and (±)-BINAP (11.7 mg, 18.8 μmol , 6.12 mol%) were dissolved in distilled Et_2O (2.00 mL) under argon and the reaction mixture was stirred for 20 min. A portion of nitroalkene standard solution (1.00 mL, 307 μmol , 1.00 eq) was added, followed by triethylaluminium (800 μL of a 1 M solution in heptane, 800 μmol , 2.61 eq) and the reaction mixture was stirred at room temperature for 23.5 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (1 mL) was added dropwise, followed by 10 % $\text{HCl}_{(\text{aq})}$ (2 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 2 mL). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification and characterisation details are given below.

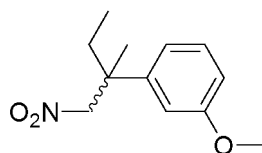
(±)-1-nitro-2-methyl-2-phenylbutane 72

Solid Cu(TC) (1.8 mg, 9.4 μmol , 3.1 mol%) and (±)-BINAP (11.3 mg, 18.1 μmol , 5.91 mol%) were dissolved in distilled Et_2O (2.00 mL) under argon and the reaction mixture was stirred for 20 min. A portion of nitroalkene standard solution (1.00 mL, 307 μmol , 1.00 eq) was added, followed by

triethylaluminium (800 μL of a 1 M solution in heptane, 800 μmol , 2.61 eq) and the reaction mixture was stirred at room temperature for 23.5 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (1 mL) was added dropwise, followed by 10 % $\text{HCl}_{(\text{aq})}$ (2 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 2 mL). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification and characterisation details are given below.

All six crude products from these reactions were combined and purification by flash column chromatography (hexane/ Et_2O 9:1, 0.3 L) gave nitroalkane (\pm)-**72** (65.8 mg, 340 μmol , 18 %) as a pale yellow oil, R_F (hexane/ Et_2O 9:1) 0.40; ^1H NMR (400 MHz, CDCl_3) δ : 7.41-7.23 (m, 5H, Ar), 4.61, 4.57 (ABq, 2H, $J_{\text{AB}} = 10.8$ Hz, CH_2NO_2), 1.98 (dq, 1H, $J = 14.0, 7.5$ Hz, $\text{CH}_3\text{CH}_a\text{H}_b$), 1.76 (dq, 1H, $J = 14.0, 7.5$ Hz, $\text{CH}_3\text{CH}_a\text{H}_b$), 1.54 (s, 3H, CH_3CPh), 0.76 (t, 3H, $J = 7.5$ Hz, CH_3CH_2); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 142.0 (Ar), 128.6 (Ar), 127.0 (Ar), 126.2 (Ar), 86.2 (CH_2NO_2), 42.7 (PhC), 32.3 (CH_3CH_2), 21.9 (PhCCH_3), 8.3 (CH_3CH_2). Spectroscopic data consistent with those reported in the literature.³⁰

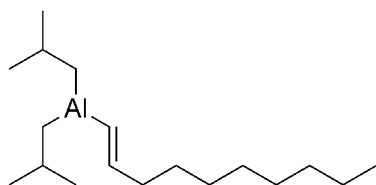
(\pm)-1-methoxy-3-(2-methyl-1-nitrobutan-2-yl)benzene 84



Solid $\text{Cu}(\text{TC})$ (1.4 mg, 7.3 μmol , 2.8 mol%) and $\text{P}(\text{OPh})_3$ (4.1 μL , 16 μmol , 6.2 mol%) were dissolved in distilled Et_2O (2.00 mL) under argon and the reaction mixture was stirred for 20 min. A solution of nitroalkene **83** (50.0 mg, 259 μmol , 1.00 eq) in Et_2O (1.00 mL) was added, followed by triethylaluminium (650 μL of a 1 M solution in heptane, 650 μmol , 2.51 eq) and the reaction mixture was stirred at room temperature for 18 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (1 mL) was added dropwise, followed by 10 % $\text{HCl}_{(\text{aq})}$ (2 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 2 mL). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by preparative

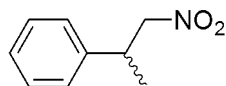
TLC (hexane/Et₂O 9:1) gave a mixture of 0.13 eq starting material plus the desired product **84** (16.4 mg, 25 %) as a pale yellow oil, ¹H NMR (400 MHz, CDCl₃) δ: 7.33-7.26 (m, 1H, Ar), 6.93-6.77 (m, 3H, Ar), 4.59, 4.56 (ABq, 2H, *J*_{AB} = 10.8 Hz, CH₂NO₂), 3.82 (s, 3H, OMe), 1.94 (dq, 1H, *J* = 14.0, 7.5 Hz, CH₃CH_aH_b), 1.74 (dq, 1H, *J* = 14.0, 7.5 Hz, CH₃CH_aH_b), 1.52 (s, 3H, CH₃C_{Ar}), 0.76 (t, 3H, *J* = 7.5 Hz, CH₃CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ: 159.7 (Ar), 143.8 (Ar), 129.5 (Ar), 118.6 (Ar), 113.2 (Ar), 111.3 (Ar), 86.1 (CH₂NO₂), 55.2 (OCH₃), 42.7 (ArC), 32.3 (CH₂CH₃), 21.9 (ArCCH₃), 8.3 (CH₂CH₃). MS and IR data not collected.

(*E*)-1-decenyl-diisobutylalane 90



An oven-dried 10 mL 2-neck round-bottomed flask equipped with stirrer, septum inlet and connection to a bubbler was flushed with argon, thermostated at 22-25 °C, and charged with 1-decyne (900 μL, 5.00 mmol, 1.00 eq) and hexane (3.20 mL). Neat DIBAL-H (890 μL, 5.00 mmol, 1.00 eq) was added dropwise with stirring *via* syringe. The reaction mixture was heated at 50 °C for 6 h, before being allowed to cool to room temperature to give (*E*)-1-decenyl-diisobutylalane **90** for use in addition reactions.

(±)-2-phenyl-1-nitropropane 91



Solid Cu(TC) (3.3 mg, 17 μmol, 3.4 mol%) and P(OPh)₃ (7.9 μL, 30 μmol, 5.9 mol%) were dissolved in distilled Et₂O (3.00 mL) under argon and the reaction mixture was stirred for 20 min. (*E*)-nitrostyrene (75.4 mg, 506 μmol, 1.00 eq) was added and the reaction mixture was cooled to −20 °C. Trimethylaluminum (630 μL of a 2 M solution in hexane, 1.26 mmol, 2.49 eq) was added and the reaction mixture was stirred at −20 °C for 19.5 h, then at room temperature for 20.5 h. Saturated NH₄Cl_(aq) (1 mL) was added dropwise, followed by 10 % HCl_(aq) (2 mL). The layers were separated and the aqueous

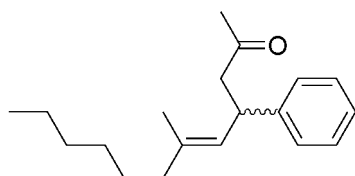
phase was extracted with Et₂O (3 x 4 mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give nitroalkane **91** (66.9 mg, 81 %) as a brown oil, *R_F* (hexane/Et₂O 9:1) 0.31; ¹H NMR (400 MHz, CDCl₃) δ: 7.40-7.35 (m, 2H, Ar), 7.33-7.24 (m, 3H, Ar), 4.61-4.49 (m, 2H, CH₂NO₂), 3.67 (app sextet, 1H, *J* = 7.9 Hz, PhCH), 1.41 (d, 3H, *J* = 7.0 Hz, CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ: 139.6 (Ar), 129.0 (Ar), 127.5 (Ar), 126.9 (Ar), 81.9 (CH₂NO₂), 38.6 (PhCH), 18.7 (CH₃); GC CP Chirasil-DEX CB, 2.5 mLmin⁻¹, 105 °C hold 5 min, 1 °Cmin⁻¹ to 115 °C, hold 1 min, 20 °Cmin⁻¹ to 180 °C, hold 2 min, 17.58 min (*ent* 1), 17.73 min (*ent* 2). Spectroscopic data consistent with those reported in the literature.³⁷

General Procedure 2: Synthesis of Scalemic 2-phenyl-1-nitropropane **91**

Copper salts (15 μmol, 3.0 mol%) and chiral ligands (30.0 μmol, 6.00 mol%) were dissolved in distilled Et₂O (3.00 mL) under argon and the solution was stirred for 20 min. (*E*)-nitrostyrene (500 μmol, 1.00 eq) was added and the reaction mixture was cooled to -10 °C. Trimethylaluminium (630 μL of a 2 M solution in hexane, 1.26 mmol, 2.50 eq) was added and the reaction mixture was stirred at -10 °C for 27 h, then at 0 °C for 21 h. The reaction was quenched with saturated NH₄Cl_(aq) (1.5 mL) followed by 10 % HCl_(aq) (3 mL), and tridecane (20 μL) was added as an internal standard. GC analysis afforded the results in **Table 2**.

5.3.2 Nickel-catalysed Tandem Coupling Reactions

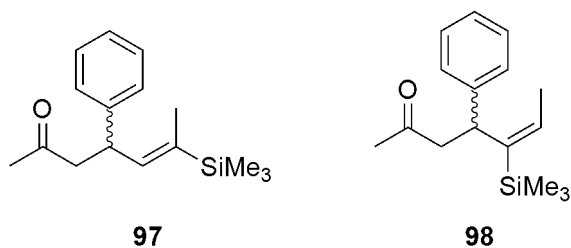
(±)-(*E*)-6-methyl-4-phenyldodec-5-en-2-one **95**



Dimethylzinc (1.20 mL of a 1.0 M solution in toluene, 1.20 mmol, 1.20 eq) was added to a solution of [Ni(acac)₂(H₂O)₂] (15.0 mg, 50.0 μmol, 5.00 mol%) and PPh₃ (13.0 mg, 50.0 μmol, 5.00 mol%) in THF (5.00 mL) at 0 °C under argon and the reaction mixture was stirred for 2 min. 1-octyne (160 μL, 1.10 mmol, 1.10 eq), benzylideneacetone (154 mg, 1.05 mmol, 1.00 eq) and

TMSCl (150 μ L, 1.20 mmol, 1.20 eq) were added at 0 $^{\circ}$ C then the reaction mixture was stirred at room temperature for 14 h. 10 % HCl_(aq) (10 mL) was added and the mixture was stirred for 10 min. The layers were separated and the aqueous phase was extracted with Et₂O (3 x 40 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄) and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (hexane/EtOAc 49:1, 0.4 L; 9:1, 0.2 L; 4:1, 0.2 L) and drying under high vacuum gave a mixture of high-boiling hexane residues and product **95** (70.0 mg, 25 %) as a colourless oil, *R*_F (hexane/EtOAc 9:1) 0.34; ¹H NMR (400 MHz, CDCl₃) δ : 7.32-7.25 (m, 2H, Ar), 7.25-7.15 (m, 3H, Ar), 5.25 (dq, 1H, *J* = 9.5, 1.5 Hz, R₂C=CHR), 4.13-4.05 (m, 1H, PhCH), 2.85-2.70 (m, 2H, COCH₂), 2.08 (s, 3H, COCH₃), 1.99-1.94 (m, 2H, CH₂), 1.67 (d, 3H, *J* = 1.5 Hz, CH₃C=C), 1.40-1.13 (m, 8H, 4 x CH₂), 0.94-0.80 (m, 3H, CH₃CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ : 207.6 (CO), 144.7, 136.7 (Ar and C=CCH₃), 128.5 (Ar), 127.1 (Ar), 126.6 and 126.1 (Ar and HC=C), 51.0 (COCH₂), 39.8 (PhC), 39.7 (C=CCH₂), 31.7 (CH₂), 30.7 (CH₃CO), 28.9 (CH₂), 27.8 (CH₂), 22.6 (CH₂), 16.4 (CH₃C=C), 14.1 (CH₂CH₃). Spectroscopic data consistent with those reported in the literature.³⁵

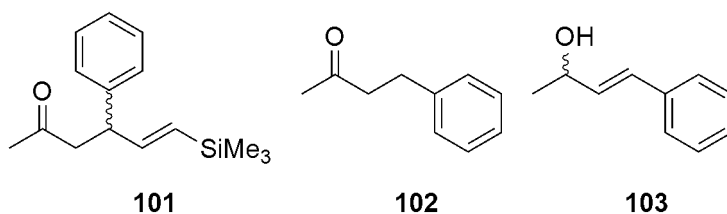
(±)-(E)-4-phenyl-6-(trimethylsilyl)hept-5-en-2-one **97**



Dimethylzinc (1.20 mL of a 1.0 M solution in toluene, 1.20 mmol, 1.20 eq) was added to a solution of Ni(acac)₂ (13.0 mg, 50.0 μ mol, 5.00 mol%) and XPhos (24.0 mg, 50.0 μ mol, 5.00 mol%) in THF (5.00 mL) at 0 $^{\circ}$ C under argon and the reaction mixture was stirred for 2 min. Trimethylsilylacetylene (160 μ L, 1.10 mmol, 1.10 eq), benzylideneacetone (147 mg, 1.00 mmol, 1.00 eq) and TMSCl (150 μ L, 1.20 mmol, 1.20 eq) were added at 0 $^{\circ}$ C then the reaction mixture was stirred at room temperature for 20 h. 10 % HCl_(aq) (10 mL) was added and the mixture was stirred for 10 min. The layers were separated and the aqueous phase was extracted with Et₂O (3 x 40 mL). The combined

organic extracts were washed with brine (50 mL), dried (MgSO₄) for 30 min and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (PE 0.6 L; PE/EtOAc 9:1, 0.4 L) gave a mixture of the desired product **97** and regioisomer **98** (34:66, 29.0 mg, 11 %) as a yellow oil, *R_F* (PE/EtOAc 9:1) 0.29; ¹H NMR (400 MHz, CDCl₃) δ: 7.40-7.20 (m, 5H, Ar), 6.03 (qd, 0.66H, *J* = 6.7, 0.7 Hz, MeCH), 5.79 (dd, 0.34H, *J* = 9.1, 1.8 Hz, CHCMe), 4.66 (0.66H, t, *J* = 7.5 Hz, PhCH), 4.30-4.20 (m, 0.34H, PhCH), 3.37-3.26 (m, 0.34H, COCH_aH_b), 3.22-3.13 (0.66H, m, COCH_aH_b), 2.89-2.62 (m, 1H, COCH_aH_b), 2.20 (s, 1.98H, CH₃CO), 2.07 (d, 1.02H, d, *J* = 1.8 Hz, CH₃CO), 1.83 (d, 1.98H, *J* = 6.7 Hz, CH₃CH), 1.76 (d, 1.02H, *J* = 1.8 Hz, CH₃CTMS), 0.04 (s, 3.06H, SiMe₃), -0.11 (s, 5.94H, SiMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ: 207.4 (CO), 144.1, 143.0, 140.4, 136.1, 128.6, 128.2, 127.6, 127.4, 126.8, 126.4, 126.3, 126.0, (Ar and alkene), 52.1, 50.6, 47.2, 40.0, 30.8, 30.6, 30.5, 15.4, (benzylic and alkyl), 0.3, -2.1, (SiMe₃); and 4-phenylpentan-2-one **99** (95.7 mg, 59 %) as a pale yellow oil, *R_F* (PE/EtOAc 9:1) 0.27; ¹H NMR (400 MHz, CDCl₃) δ: 7.34-7.26 (m, 2H, Ar), 7.25-7.17 (m, 3H, Ar), 3.37-3.27 (m, 1H, PhCH), 2.77 (dd, 1H, *J* = 16.1, 6.1 Hz, CH₃COCH_aH_b), 2.69 (dd, 1H, *J* = 16.1, 7.9 Hz, CH₃COCH_aH_b), 2.08 (s, 3H, CH₃CO), 1.28 (d, 3H, *J* = 7.0 Hz, CH₃CH); ¹³C NMR (100.6 MHz, CDCl₃) δ: 207.8 (CO), 146.1 (Ar), 128.5 (Ar), 126.7 (Ar), 126.3 (Ar), 52.0 (COCH₂), 35.4 (PhCH), 30.5 (COCH₃), 22.0 (CHCH₃). Spectroscopic data consistent with those reported in the literature.¹⁵⁰

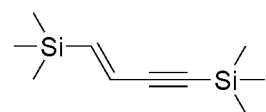
4-phenylbutan-2-one **102**



Solid *i*Pr₂NAIH₂ (155 mg, 1.20 mmol, 1.17 eq) was added to a solution of [Ni(acac)₂(H₂O)₂] (14.7 mg, 50.2 μmol, 4.87 mol%) and PPh₃ (13.5 mg, 51.5 μmol, 5.00 mol%) in THF (5.00 mL) at 0 °C under argon and the reaction mixture was stirred for 2 min. Trimethylsilylacetylene (160 μL, 1.10 mmol, 1.07 eq), benzylideneacetone (150 mg, 1.03 mmol, 1.00 eq) and TMSCl (150

μL , 1.20 mmol, 1.17 eq) were added at 0 °C then the reaction mixture was stirred at room temperature for 18 h. Aqueous 10 % HCl (10 mL) was added and the mixture was stirred for 10 min. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO_4) for 30 min and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (pentane, 0.4 L; PE/ Et_2O 2:1, 0.6 L) failed to yield the desired product **101**, but gave 4-phenylbutan-2-one **102** (45.2 mg, 29 %) as an amber oil, R_F (PE/ Et_2O 2:1) 0.47; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.32-7.26 (m, 2H, Ar), 7.24-7.16 (m, 3H, Ar), 2.94-2.88 (m, 2H, CH_2CO), 2.80-2.75 (m, 2H, PhCH_2), 2.15 (s, 3H, CH_3); $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ : 207.9 (CO), 141.0 (Ar), 128.5 (Ar), 128.3 (Ar), 126.1 (Ar), 45.2 (COCH_2), 30.1 (PhC), 29.7 (CH_3); and (*E*)-4-phenylbut-3-en-2-ol **103** (impure, 195 mg) as an amber oil, R_F (PE/ Et_2O 2:1) 0.15; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.42-7.37 (m, 2H, Ar), 7.36-7.19 (m, 3H, Ar), 6.59 (d, 1H, $J = 15.8$ Hz, PhCH), 6.28 (dd, 1H, $J = 15.8$, 6.4 Hz, PhCHCH), 4.55-4.47 (m, 1H, CH_3CH), 1.39 (d, 3H, $J = 6.4$ Hz, CH_3), OH not observed; $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ : 137.3 (Ar), 133.5 (PhCHCH), 129.4 (PhCH), 128.6 (Ar), 127.6 (Ar), 126.4 (Ar), 69.0 (CHOH), 23.4 (CH_3). Spectroscopic data consistent with those reported in the literature.^{151,152}

(*E*)-but-1-en-3-yne-1,4-diylbis(trimethylsilane) 100

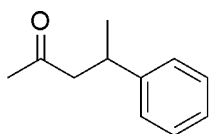


Dimethylzinc (1.25 mL of a 1.0 M solution in toluene, 1.25 mmol, 1.10 eq) was added to a solution of $[\text{Ni}(\text{acac})_2(\text{H}_2\text{O})_2]$ (14.7 mg, 50.2 μmol , 4.56 mol%) and PPh_3 (13.2 mg, 50.3 μmol , 4.57 mol%) in THF (5.00 mL) at 0 °C under argon and the reaction mixture was stirred for 2 min. Trimethylsilylacetylene (160 μL , 1.10 mmol, 1.00 eq) and TMSCl (150 μL , 1.20 mmol, 1.10 eq) were added at 0 °C then the reaction mixture was stirred at room temperature for 20.5 h. Aqueous 10 % HCl (10 mL) was added and the mixture was stirred for 10 min. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine

(50 mL), dried (MgSO₄) for 30 min and concentrated under reduced pressure to give dimer **100** (26.5 mg, 24 %), *R_F* (PE) 0.50; ¹H NMR (400 MHz, CDCl₃) δ: 6.53 (d, 1H, *J* = 19.3 Hz, CH), 5.98 (d, 1H, *J* = 19.3 Hz, CH), 0.20 (s, 9H, SiMe₃), 0.08 (s, 9H, SiMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ: 191.4 (CH), 147.0 (CH), 123.3 (C), 105.3 (C), -0.1 (CH₃), -1.7 (CH₃). Spectroscopic data consistent with those reported in the literature.¹⁵³

5.3.3 Nickel-catalysed Conjugate Methyl Addition to Benzylideneacetone

General Procedure 3: Synthesis of 4-phenylpentan-2-one **99**



Nickel salts (25 μmol, 5.0 mol%) and chiral ligands (25.0 μmol, 5.00 mol%) were dissolved in ether solvent (2.50 mL). At 0 °C under argon, organometallic methyl source (600 μmol, 1.20 eq) was added and the solution was stirred for 2 min. Benzylideneacetone (73.0 mg, 500 μmol, 1.00 eq) was added at 0 °C then the reaction mixture was stirred at 20 °C for 1 h. Tridecane (20.0 μL) was added as an internal standard for GC analysis, and 1 M HCl_(aq) was added until evolution ceased. A sample of the organic phase was filtered through a Pasteur pipette of silica, washing with CH₂Cl₂. The resulting solution (5 drops) was diluted with Et₂O (1 mL) in a GC vial and analysed by GC ((2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin, 2.0 mLmin⁻¹, 75 °C hold 10 min, 1 °Cmin⁻¹ to 110 °C), (*ent 1*) 27.05 min, (*ent 2*) 29.04 min.

General Procedure 4: Synthesis of 4-phenylpentan-2-one **99**

Benzylideneacetone (292 mg, 2.00 mmol) was dissolved in solvent (2.00 mL) to give a 1.0 M standard solution. Nickel salts (25 μmol, 5.00 mol%) and chiral ligands (25.0 μmol, 5.00 mol%) were dissolved in ether solvent (2.00 mL). At 0 °C under argon, organometallic methyl source (600 μmol, 1.20 eq) was added and the solution was stirred for 2 min. A portion of benzylideneacetone standard solution (500 μL, 500 μmol, 1.00 eq) was added at 0 °C then the reaction mixture was stirred at 20 °C for 1 h. Tridecane (20.0 μL) was added as an internal standard for GC analysis, and 1 M HCl_(aq) was added until evolution

ceased. A sample of the organic phase was filtered through a Pasteur pipette of silica, washing with CH_2Cl_2 . 5 drops of the resulting solution were diluted with Et_2O (1 mL) in a GC vial and analysed by GC ((2,6-di-*O*-methyl-3-*O*-pentyl)- γ -cyclodextrin, 2.0 mLmin^{-1} , 75°C hold 10 min, 1°Cmin^{-1} to 110°C), (*ent 1*) 27.05 min, (*ent 2*) 29.04 min.

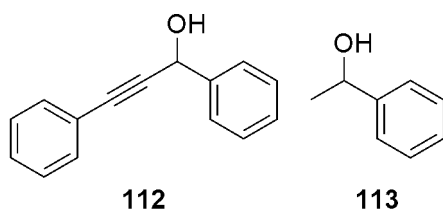
4-phenylpentan-2-one **99**

Using General Procedure **3**, Hayashi diene ligand **109** (8.2 mg, 25 μmol), $\text{Ni}(\text{acac})_2$ (6.2 mg, 24 μmol), Me_2Zn (610 μL of a 1.0 M solution in toluene, 610 μmol) and THF gave product **99** (98 %, 50:50 er).

5.3.4 Conjugate Addition of Alkynylaluminium Reagents to Acyclic Enones

5.3.4.1 Nickel-catalysed Conjugate Addition of Alkynylaluminium to Acyclic Enones

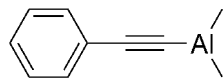
General Procedure 5: Synthesis of 1,3-diphenylprop-2-yn-1-ol **112**



A flame-dried, stirrer-equipped Schlenk tube under argon was charged with Me_3Al (1.00 mL of a 2.0 M solution in hexane, 2.00 mmol, 1.00 eq). Heptamethyldisilazane (40.0-120 μmol , 2.00-6.00 mol%) and phenylacetylene (2.00-2.40 mmol, 1.00-1.20 eq) were added and the reaction mixture was stirred at a given temperature for 5-20 h. Distilled benzaldehyde (200 μL , 2.00 mmol, 1.00 eq) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was pipetted onto a cooled 2 M aqueous solution of Rochelle's salt (5 mL), and the Schlenk tube was washed with Et_2O (3 x 3 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give the crude product as a

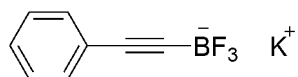
mixture of the desired product **112**, methyl addition product **113**, phenylacetylene, and benzaldehyde.

Dimethyl(phenylethynyl)aluminium 111



A flame-dried, stirrer-equipped Schlenk tube under argon was charged with Me₃Al (12.0 mL of a 2.0 M solution in hexane, 24.0 mmol, 1.00 eq). Heptamethyldisilazane (360 µL, 1.44 mmol, 6.00 mol%) and phenylacetylene (3.15 mL, 28.8 mmol, 1.20 eq) were added and the reaction mixture was stirred at 40 °C for 5 h, then at room temperature for a further 2.5 h. The resulting solution was then used in conjugate addition reactions.

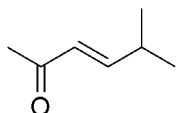
Potassium (phenylethynyl)trifluoroborate 115



A solution of phenylacetylene (1.10 mL, 10.0 mmol, 1.00 eq) in dry THF (20.0 mL) was cooled to -78 °C under argon. A solution of *n*BuLi (6.25 mL of a 1.6 M solution in hexane, 10.0 mmol, 1.00 eq) was added dropwise and the solution was stirred for 1 h at this temperature. Trimethylborate (1.65 mL, 15.0 mmol, 1.50 eq) was added dropwise at -78 °C and the solution was stirred at this temperature for a further 1 h. The solution was then allowed to warm to -20 °C for 1 h and a saturated aqueous solution of potassium hydrogen fluoride (4.67 g, 59.8 mmol, 5.98 eq) was added to the vigorously stirred solution. The resulting mixture was stirred at -20 °C for 1 h then allowed to warm to room temperature for 1 h. The organic solvent was removed under reduced pressure and the aqueous phase was filtered to give the crude product. The wet solid was dried under high vacuum (4 h), washed with acetone (10 mL) then hot acetone (10 mL), and the solvent was removed under reduced pressure to give a fluffy white solid. Redissolving in hot acetone and precipitation with Et₂O before cooling to -20 °C and Büchner filtration afforded product **115** (879 mg, 42 %) as a white crystalline solid, ¹H NMR (400 MHz, Acetone-d₆) δ: 7.31-7.26 (m, 2H, Ar), 7.23-7.12 (m, 3H, Ar); ¹³C NMR (100.6 MHz,

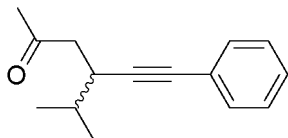
Acetone-d₆) δ : 132.0 (Ar), 128.7 (Ar), 127.1 (Ar). Spectroscopic data consistent with those reported in the literature.¹⁵⁴

General Procedure 6: Purification of (*E*)-5-methylhex-3-en-2-one **114**



Technical grade (*E*)-5-methylhex-3-en-2-one (5.04 g, 44.9 mmol, 75 % mixture with 25 % isomeric 5-methylhex-4-en-2-one) was dissolved in CH₂Cl₂ (10.0 mL) and solid *m*CPBA (2.12 g, 80 % wt, 9.81 mmol) was added at 0 °C. The solution was stirred for 30 min, before a solution of sodium sulfite (2.00 g) in H₂O (10 mL) was added. Stirring was continued for a further 5 min, saturated NaHCO_{3(aq)} (10 mL) was added and the layers were separated. The organic phase was dried (MgSO₄) and evaporated under reduced pressure to give the crude mixture of desired compound and epoxidised isomer as a pale yellow oil. Purification by flash column chromatography (PE/Et₂O 4:1, 1.0 L) gave enone **114** (2.72 g, 66 %) as a pale yellow oil, *R*_F (PE/Et₂O 4:1) 0.38; ¹H NMR (400 MHz, CDCl₃) δ : 6.76 (dd, 1H, *J* = 16.1, 6.7 Hz, ^{*i*}PrCH), 6.03 (dd, 1H, *J* = 16.1, 1.5 Hz, CH₃C(O)CH), 2.54-2.40 (m, 1H, (CH₃)₂CH), 2.25 (s, 3H, CH₃CO), 1.08 (d, 6H, *J* = 6.7 Hz, (CH₃)₂CH); ¹³C NMR (100.6 MHz, CDCl₃) δ : 199.1 (CO), 154.5 (CHCHCO), 128.5 (CHCHCO), 31.1 ((CH₃)₂CH), 26.9 (COCH₃), 21.3 (2 x CHCH₃). Spectroscopic data consistent with those in the literature.¹⁵⁵

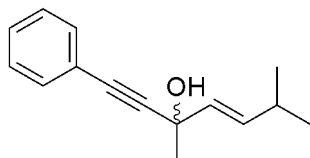
(±)-5-methyl-4-(phenylethynyl)hexan-2-one **116**



Liquid BF₃.OEt₂ (380 μ L, 3.00 mmol, 1.50 eq) was added at 0 °C under argon to a stirred suspension of potassium (phenylethynyl)trifluoroborate **115** (824 mg, 3.96 mmol, 1.98 eq) in CH₂Cl₂ (20.0 mL). To the mixture was added a solution of (*E*)-5-methylhex-3-en-2-one **114** (270 μ L, 2.00 mmol, 1.00 eq) in CH₂Cl₂ (5.00 mL) at room temperature, and the reaction mixture was stirred for 4 h at room temperature. The reaction was quenched with brine (15 mL)

then diluted with CH₂Cl₂ (10 mL). The layers were separated and the organic layer dried (MgSO₄) before evaporation under reduced pressure to give the crude product. Purification by flash column chromatography (pentane/Et₂O 9:1, 1.0 L; Et₂O 0.1 L) gave product **116** (265 mg, 62 %) as a red-orange oil, *R*_F (pentane/EtOAc 9:1) 0.38; **IR** (CHCl₃) 3689, 2965, 1713, 1490, 1303, 1163 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 7.41-7.36 (m, 2H, Ar), 7.30-7.25 (m, 3H, Ar), 3.07-3.01 (m, 1H, (CH₃)₂CH), 2.78-2.72 (m, 1H, CH₃COCH_aH_b), 2.61-2.56 (m, 1H, CH₃COCH_aH_b), 2.24 (s, 3H, CH₃CO), 1.85-1.76 (m, 1H, CH₃COCH₂CH), 1.07 (d, 3H, *J* = 6.7 Hz, (CH₃)_a(CH₃)_bCH), 1.03 (d, 3H, *J* = 6.7 Hz, (CH₃)_a(CH₃)_bCH); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 207.1 (CO), 131.6 (Ar), 128.1 (Ar), 127.6 (Ar), 123.7 (Ar), 90.3 (PhCC), 83.0 (PhC), 46.8 (COCH₂), 34.5 (PhCCCH), 31.5 ((CH₃)₂CH), 30.6 (COCH₃), 21.1 ((C_aH₃)(C_bH₃)CH), 18.2 ((C_aH₃)(C_bH₃)CH); **HRMS** (ESI, pos.), *m/z* for C₁₅H₁₈O ([M + Na]⁺), calcd. 237.1255, found 237.1257; **GC** Octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin, 2.5 mLmin⁻¹, 70 °C hold 5 min, 1 °Cmin⁻¹ to 140 °C, hold 15 min, 5 °Cmin⁻¹ to 175 °C, hold 15 min: 64.86 min (*ent* 1), 65.39 min (*ent* 2).

(±)-(E)-3,6-dimethyl-1-phenylhept-4-en-1-yn-3-ol 117



A solution of phenylacetylene (440 μL, 4.00 mmol, 1.00 eq) in Et₂O (9.00 mL) was added dropwise with stirring to ethylmagnesium bromide (1.35 mL of a 3 M solution in Et₂O, 4.00 mmol, 1.00 eq) under argon. The reaction mixture was heated at reflux for 40 min, then allowed to cool to room temperature. A solution of (*E*)-5-methylhex-3-en-2-one **114** (450 μL, 3.33 mmol, 83.3 mol%) in Et₂O (5.50 mL) was added to the resulting pale yellow solution, and the reaction mixture was stirred at room temperature for 3.5 h. The reaction was quenched with saturated NH₄Cl_(aq), the layers were separated and the aqueous phase was extracted with Et₂O (3 x 5 mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (pentane/Et₂O 9:1,

0.8 L) gave enol **117** (375 mg, 52 %) as a yellow oil, **R_F** (pentane/EtOAc 9:1) 0.28; **IR** (CHCl₃) 3690, 3594, 3012, 2964, 2360, 1601, 1490, 1239 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 7.50-7.43 (m, 2H, Ar), 7.35-7.30 (m, 3H, Ar), 6.02 (dd, 1H, *J* = 15.3, 6.5 Hz, ^{*i*}PrCH=CH), 5.63 (dd, 1H, *J* = 15.3, 1.3 Hz, ^{*i*}PrCH=CH), 2.36 (septdd, 1H, *J* = 6.8, 6.5, 1.3 Hz, (CH₃)₂CH), 2.09 (br s, 1H, OH), 1.65 (s, 3H, CH₃COH), 1.04 (d, 6H, *J* = 6.8 Hz, (CH₃)₂CH); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 137.5 (^{*i*}PrCH), 131.7 (^{*i*}PrCHCH), 131.2 (Ar), 128.3 (Ar), 128.2 (Ar), 122.7 (Ar), 91.7 (PhCC), 84.5 (PhC), 68.4 (COH), 30.9 (COHCH₃), 30.6 ((CH₃)₂CH), 22.2 ((CH₃)₂CH); **HRMS** (ESI, pos.), *m/z* for C₁₅H₁₈O ([M + Na]⁺), calcd. 237.1255, found 237.1252; **GC** Octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin, 2.5 mLmin⁻¹, 70 °C hold 5 min, 1 °Cmin⁻¹ to 140 °C, hold 15 min, 5 °Cmin⁻¹ to 175 °C, hold 15 min: 68.26 min. Enantiomers were not split.

General Procedure 7: Screening of Background Reaction in Various Solvents

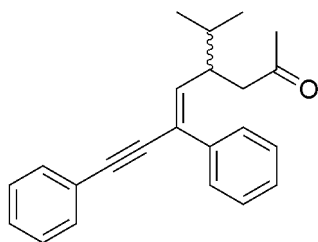
A flame-dried, stirrer-equipped Schlenk tube under argon was charged with Me₃Al (1.00 mL of a 2.0 M solution in hexane, 2.00 mmol, 2.50 eq). Heptamethyldisilazane (30.0 μL, 120 μmol, 15.0 mol%) and phenylacetylene (260 μL, 2.40 mmol, 3.00 eq) were added and the reaction mixture was stirred at 25 °C for 16.5 h. Freshly distilled solvent (3.00 mL) was added and the solution was cooled to -45 °C. (*E*)-5-methylhex-3-en-2-one **114** (108 μL, 800 μmol, 1.00 eq) was added and the reaction mixture was stirred at -45 °C for 4 h. 1 M HCl_(aq) was added and the reaction mixture transferred to a round-bottomed flask with stirring. The Schlenk tube was washed with CH₂Cl₂ (3 x 3 mL) and the washings were added to the flask. The layers were separated, the aqueous phase was extracted with CH₂Cl₂ (3 x 5 mL) and the organic extracts were dried (MgSO₄). Evaporation under reduced pressure gave the crude product, which was analysed by ¹H NMR spectroscopy.

General Procedure 8: Screening of Background Nickel-Catalysed Reaction

A flame-dried, stirrer-equipped Schlenk tube under ar was charged with Me₃Al (1.00 mL of a 2.0 M solution in hexane, 2.00 mmol, 2.50 eq).

Heptamethyldisilazane (30.0 μ L, 120 μ mol, 15.0 mol%) and phenylacetylene (260 μ L, 2.40 mmol, 3.00 eq) were added and the reaction mixture was stirred at 40 °C for 5 h. In a separate Schlenk tube, nickel salts (72.0 μ mol, 9.00 mol%) were dissolved in freshly distilled solvent (3.00 mL) under argon and the solution was cooled to -45 °C. The alkynylaluminium solution was added, followed by (*E*)-5-methylhex-3-en-2-one **114** (108 μ L, 800 μ mol, 1.00 eq) and the reaction mixture was stirred at -45 °C for 16 h. 1 M HCl_(aq) was added and the reaction mixture transferred to a round-bottomed flask with stirring. The Schlenk tube was washed with CH₂Cl₂ (3 x 3 mL) and the washings were added to the flask. The layers were separated, the aqueous phase was extracted with CH₂Cl₂ (3 x 5 mL) and the organic extracts were dried (MgSO₄). Evaporation under reduced pressure gave the crude product.

(±)-(Z)-4-isopropyl-6,8-diphenyloct-5-en-7-yn-2-one **121**



Using General Procedure **8**, Ni(acac)₂ (18.7 mg, 72.8 μ mol, 9.10 mol%) and THF (3.00 mL) and purification by flash column chromatography (pentane/EtOAc, 9:1, 0.8 L) gave **121** (123 mg, 49 %) as a yellow oil, *R*_F (pentane/EtOAc 9:1) 0.40; *IR* (CHCl₃) 3692, 2963, 1705, 1599, 1490, 1361 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.68-7.62 (m, 2H, Ar), 7.57-7.51 (m, 2H, Ar), 7.40-7.33 (m, 5H, Ar), 7.32-7.29 (m, 1H, Ar), 6.29 (d, 1H, *J* = 10.2 Hz, CH=CPhC), 3.40-3.31 (m, 1H, (CH₃)₂CH), 2.74-2.69 (m, 1H, CH₃COCH_aH_b), 2.56-2.50 (m, 1H, CH₃COCH_aH_b), 2.20 (s, 3H, CH₃CO), 1.95-1.83 (m, CH₃COCH₂CH), 1.02 (d, 3H, *J* = 6.7 Hz, (CH₃)_a(CH₃)_bCH), 0.99 (d, 3H, *J* = 6.7 Hz, (CH₃)_a(CH₃)_bCH); ¹³C NMR (100.6 MHz, CDCl₃) δ : 208.3 (CO), 139.1 (C=CH), 138.0 (Ar), 131.5 (Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 126.2 (Ar), 124.9 (C=CH), 95.2 (PhC), 86.8 (PhCC), 47.3 (COCH₂), 43.8 (*i*PrCH), 32.6 ((CH₃)₂CH), 29.9 (COCH₃), 20.8 ((C_aH₃)(C_bH₃)CH), 19.2 ((C_aH₃)(C_bH₃)CH); *HRMS* (ESI, pos.), *m/z* for C₂₃H₂₄O ([M + Na]⁺), calcd. 339.1725, found 339.1709.

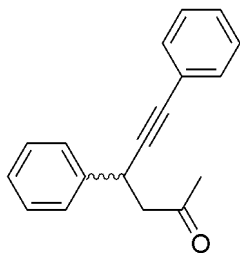
General Procedure 9: Ligand and Nickel Source Screening

A flame-dried, stirrer-equipped Schlenk tube under argon was charged with Me₃Al (12.0 mL of a 2.0 M solution in hexane, 24.0 mmol, 1.00 eq). Heptamethyldisilazane (360 µL, 1.40 mmol, 6.00 mol%) and phenylacetylene (3.15 mL, 28.8 mmol, 1.20 eq) were added and the reaction mixture was stirred at 40 °C for 5 h. In a separate Schlenk tube, nickel salts (72.0 µmol, 9.00 mol%) and ligands (72.0 µmol, 9.00 mol%) were dissolved in solvent (3.00 mL) under argon and heated at reflux for 1 h. The resulting solution was allowed to cool to room temperature, then cooled to −45 °C. A portion of the alkynylaluminium solution (1.30 mL, 2.00 mmol, 2.50 eq) was added, followed by (*E*)-5-methylhex-3-en-2-one (108 µL, 800 µmol, 1.00 eq) and the reaction mixture was stirred at −45 °C for 18 h. Tridecane (20-40 µL depending on calibration) was added, followed by 1 M HCl_(aq) (3 mL) and the reaction mixture was stirred at room temperature until gas evolution ceased. A sample of the organic phase was filtered through a Pasteur pipette of silica and 5 drops were diluted with Et₂O (1 mL) in a GC vial. The results of the GC analysis are shown in **Table 4**.

General Procedure 10: Screening of Transition Metal Catalysts

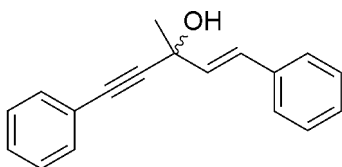
A flame-dried, stirrer-equipped Schlenk tube under argon was charged with Me₃Al (12.0 mL of a 2.0 M solution in hexane, 24.0 mmol, 1.00 eq). Heptamethyldisilazane (360 µL, 1.40 mmol, 6.00 mol%) and phenylacetylene (3.15 mL, 28.8 mmol, 1.20 eq) were added and the reaction mixture was stirred at 40 °C for 5 h. In a separate Schlenk tube, transition metal salts (72.0 µmol, 9.00 mol%) and (*R,S*)-Josiphos (46.0 mg, 72.0 µmol, 9.00 mol%) were dissolved in Et₂O (3.00 mL) under argon at −45 °C. A portion of the alkynylaluminium solution (1.10 mL, 2.00 mmol, 2.50 eq) was added, followed by (*E*)-5-methylhex-3-en-2-one (100 µL, 741 µmol, 1.00 eq) and the reaction mixture was stirred at −45 °C for 16 h. Tridecane (40 µL) was added, followed by 1 M HCl_(aq) (3 mL) and the reaction mixture was stirred at room temperature until gas evolution ceased. A sample of the organic phase was filtered through a Pasteur pipette of silica, washing with CH₂Cl₂ (1 mL), and 5 drops were diluted with Et₂O (1 mL) in a GC vial. The results of the GC analysis are shown in **Table 5**.

(±)-4,6-Diphenylhex-5-yn-2-one 119



Liquid $\text{BF}_3 \cdot \text{OEt}_2$ (190 μL , 1.50 mmol, 1.53 eq) was added to a stirred suspension of potassium (phenylethynyl)trifluoroborate (413 mg, 1.99 mmol, 2.03 eq) in CH_2Cl_2 (10.0 mL) at 0 °C under argon. A solution of benzylideneacetone (143 mg, 980 μmol , 1.00 eq) in CH_2Cl_2 (2.50 mL) was added at room temperature and the reaction mixture was stirred for 25 min. Brine (7 mL) and CH_2Cl_2 (5 mL) were added, the layers were separated and the organic phase was dried (MgSO_4). The solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography (pentane/ Et_2O 9:1, 0.6 L; Et_2O 0.2 L) gave **119** (109 mg, 45 %) as an amber oil, R_F (pentane/ Et_2O 9:1) 0.23; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.48-7.24 (m, 10H, Ar), 4.45-4.40 (m, 1H, PhCH), 3.08 (dd, 1H, $J = 16.4, 8.0$ Hz, $\text{CH}_a\text{H}_b\text{CO}$), 2.90 (dd, 1H, $J = 16.4, 6.3$ Hz, $\text{CH}_a\text{H}_b\text{CO}$), 2.19 (s, 3H, CH_3); $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ : 206.0 (CO), 140.9 (Ar), 131.6 (Ar), 128.7 (Ar), 128.2 (Ar), 128.0 (Ar), 127.4 (Ar), 127.1 (Ar), 123.3 (Ar), 90.3 (PhCC), 83.3 (PhCC), 51.9 (CH_2), 33.5 (PhCH), 30.6 (CH_3). Data were consistent with literature values.⁴⁹

(±)-3-methyl-1,5-diphenylpent-1-en-4-yn-3-ol 120

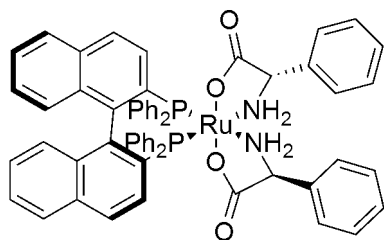


A solution of phenylacetylene (440 μL , 4.00 mmol, 1.00 eq) in Et_2O (9.00 mL) was added dropwise with stirring to EtMgBr (1.35 mL of a 3 M solution in Et_2O , 4.00 mmol, 1.00 eq), and the reaction mixture was heated at reflux for 40 min then allowed to cool to room temperature. A solution of benzylideneacetone (581 mg, 3.98 mmol, 1.00 eq) in Et_2O (5.50 mL) was added dropwise and the reaction mixture was stirred at room temperature for

3.5 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL) was added, the layers were separated and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (pentane/ Et_2O 9:1, 1.0 L) gave **120** (211 mg, 21 %) as a yellow oil, R_F (pentane/ Et_2O 9:1) 0.09; ^1H NMR (400 MHz, CDCl_3) δ : 7.51-7.23 (m, 10H, Ar), 6.96 (d, 1H, J = 15.8 Hz, $\text{PhCH}=\text{CH}$), 6.40 (d, 1H, J = 15.8 Hz, $\text{PhCH}=\text{CH}$), 2.25 (br s, 1H, OH), 1.77 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 136.2 (Ar), 133.3 ($\text{PhCH}=\text{CH}$), 131.7 (Ar), 129.2 ($\text{PhCH}=\text{CH}$), 128.6 (Ar), 128.5 (Ar), 128.3 (Ar), 127.9 (Ar), 126.8 (Ar), 122.5 (Ar), 91.0 (CC), 85.0 (CC), 68.5 (COH), 30.5 (CH_3). Data were consistent with literature values.¹⁵⁶

5.3.4.2 Application of Ruthenium-catalysed Hydrocyanation Conditions to Alkynylaluminium Conjugate Addition

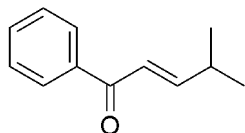
[Ru{(S)-PhGly}₂]{(S)-BINAP} **129**



Under argon, a flame-dried, stirrer-equipped Schlenk tube was charged with $[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$ (124 mg, 247 μmol , 1.00 eq) and (S)-BINAP (312 mg, 500 μmol , 2.02 eq). Dimethylformamide (7.50 mL) was added *via* syringe under a stream of argon and the reaction mixture was stirred at 100 °C for 10 min then cooled to 25 °C. A powder of (S)-phenylglycine (755 mg, 5.00 mmol) was dissolved in $\text{NaOH}_{(\text{aq})}$ (0.103 M, 50.0 mL, 5.15 mmol) and the solvent was evaporated under high vacuum to give sodium (S)-phenylglycinate (773 mg, 89 %) as a white powder. In a Schlenk tube, sodium (S)-phenylglycinate (259 mg, 1.50 mmol, 6.07 eq) was dissolved in MeOH (15.0 mL) and the solution was degassed, and then added to the Ru/BINAP solution *via* syringe under a stream of argon. The resulting light red solution was stirred at 25 °C for 16 h and H_2O (25 mL) was added with vigorous stirring. The resulting yellow/orange precipitate was filtered off and

redissolved in CH₂Cl₂ (20 mL). The solution was washed with H₂O (3 x 25 mL) and dried (MgSO₄). Filtration through a pad of Celite[®] and concentration under reduced pressure gave the crude product. Purification by flash column chromatography under argon (EtOAc, 0.5 L) gave **129** (380 mg, 74 %) as a yellow/orange powder, *R*_F (EtOAc) 0.39; ¹H NMR (400 MHz, CDCl₃) δ: 8.20-7.95 (m, 4H, Ar), 7.70-7.50 (m, 12H, Ar), 7.25-7.10 (m, 12H, Ar), 6.80-6.70 (m, 6H, Ar), 6.60-6.45 (m, 6H, Ar), 6.25 (d, 2H, *J* = 8.5 Hz, Ar), 3.66 (t, 2H, *J* = 8.0 Hz, 2 x PhCH), 3.28-3.24 (m, 2H, 2 x NH_aH_b), 2.40 (t, 2H, *J* = 10.0 Hz, 2 x NH_aH_b); ³¹P NMR (162 MHz, CDCl₃) δ: 50.18 (s). Data were consistent with literature values.⁶⁸

(*E*)-4-methyl-1-phenyl-2-penten-1-one 131



In a flame-dried, stirrer-equipped round-bottomed flask under argon, diisopropylamine (2.95 mL, 21.0 mmol, 1.05 eq) was added to THF (32.0 mL) and the flask was cooled to -20 °C. A solution of ⁿBuLi (13.0 mL of a 1.6 M solution in hexanes, 20.8 mmol, 1.05 eq) was added with stirring, and the reaction mixture was stirred at -20 °C for 30 min. The reaction mixture was cooled to -78 °C and acetophenone (2.35 mL, 20.0 mmol, 1.00 eq) was added, before stirring at -78 °C for 30 min. Isobutyraldehyde (2.00 mL, 22.0 mmol, 1.10 eq) was added and stirring was continued at -78 °C for 30 min. Saturated NaHCO_{3(aq)} (13 mL) was added and the mixture was allowed to come to room temperature. The layers were separated and the aqueous phase was extracted with Et₂O (2 x 20 mL). The combined organic extracts were washed with cold 1 % HCl_(aq) (24 mL), saturated NaHCO_{3(aq)} (24 mL) and brine (24 mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a pale yellow oil. The oil was dissolved in pyridine (15.0 mL) under argon at 0 °C, and mesyl chloride (1.55 mL, 20.0 mmol, 1.00 eq) was added. The reaction mixture was stirred at 0 °C for 16 h, H₂O (40 mL) was added and the mixture was extracted with Et₂O (3 x 30 mL). The combined organic extracts were washed with saturated CuSO_{4(aq)} (4 x 20 mL) and brine (30 mL), and dried (Na₂SO₄). Evaporation of the solvent under reduced pressure gave an amber oil. The oil was redissolved

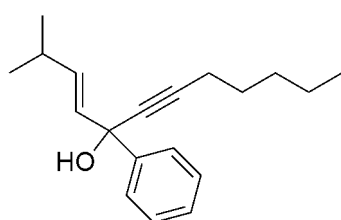
in Et₂O (50.0 mL) and Et₃N (2.90 mL, 20.8 mmol, 1.04 eq) was added. The mixture was stirred at room temperature for 18 h, H₂O (20 mL) was added and the mixture was stirred for 10 min. The layers were separated and the organic phase was washed with cold 1 % HCl_(aq) (24 mL), saturated NaHCO_{3(aq)} (20 mL) and brine (20 mL), dried (Na₂SO₄) and evaporated *in vacuo* to give the crude product. Purification by flash column chromatography (pentane/EtOAc 10:1, 0.77 L) gave **131** (2.11 g, 60 %) as a yellow oil, *R*_F (pentane/EtOAc 10:1) 0.53; ¹H NMR (400 MHz, CDCl₃) δ: 7.96-7.90 (m, 2H, Ar), 7.59-7.53 (m, 1H, Ar), 7.52-7.44 (m, 2H, Ar), 7.04 (dd, 1H, *J* = 15.4, 6.7 Hz, ^{*i*}PrCH=CH), 6.83 (dd, 1H, *J* = 15.4, 1.1 Hz, ^{*i*}PrCH=CH), 2.64-2.52 (m, 1H, CH(CH₃)₂), 1.15 (d, 6H, *J* = 6.8 Hz, 2 x CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ: 191.3 (CO), 156.0 (^{*i*}PrCH=CH), 138.1 (Ar), 132.5 (Ar), 128.5 (Ar), 128.5 (Ar), 123.1 (^{*i*}PrCH=CH), 31.5 (CH(CH₃)₂), 21.4 (CH₃). Data were consistent with literature values.⁴⁷

(*E*)-4-methyl-1-phenyl-2-penten-1-one 131

In a flame-dried, stirrer-equipped round-bottomed flask under argon, diisopropylamine (5.90 mL, 42.0 mmol, 1.05 eq) was added to THF (64.0 mL) and the flask was cooled to -20 °C. A solution of ^{*n*}BuLi (26.0 mL of a 1.6 M solution in hexanes, 41.6 mmol, 1.05 eq) was added with stirring, and the reaction mixture was stirred at -20 °C for 30 min. The reaction mixture was cooled to -78 °C and acetophenone (4.70 mL, 40.3 mmol, 1.00 eq) was added, before stirring at -78 °C for 30 min. Isobutyraldehyde (4.00 mL, 43.8 mmol, 1.10 eq) was added and stirring was continued at -78 °C for 30 min. Saturated NaHCO_{3(aq)} (26 mL) was added and the mixture was allowed to come to room temperature. The layers were separated and the aqueous phase was extracted with Et₂O (2 x 40 mL). The combined organic extracts were washed with cold 1 % HCl_(aq) (48 mL), saturated NaHCO_{3(aq)} (48 mL) and brine (48 mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a pale yellow oil. The oil was dissolved in pyridine (30 mL) under argon at 0 °C, and mesyl chloride (3.10 mL, 40.0 mmol, 1.00 eq) was added. The reaction mixture was stirred at 0 °C for 16 h, H₂O (80 mL) was added and the mixture was extracted with Et₂O (3 x 60 mL). The combined organic extracts were washed with saturated CuSO_{4(aq)} (4 x 40 mL) and brine (60 mL), and dried (Na₂SO₄). Evaporation of

the solvent under reduced pressure gave an amber oil. The oil was redissolved in Et₂O (100 mL) and Et₃N (5.80 mL, 41.6 mmol, 1.04 eq) was added. The mixture was stirred at room temperature for 18 h, H₂O (40 mL) was added and the mixture was stirred for 10 min. The layers were separated and the organic phase was washed with cold 1 % HCl_(aq) (48 mL), saturated NaHCO_{3(aq)} (40 mL) and brine (40 mL), dried (Na₂SO₄) and evaporated *in vacuo* to give the crude product. Purification by vacuum distillation gave **131** (5.54 g, 79 %) as a pale yellow oil. Data as above.

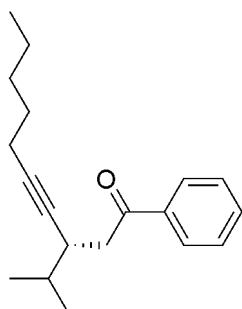
(E)-2-methyl-5-phenyldodec-3-en-6-yn-5-ol 133



A flame-dried, stirrer-equipped Schlenk tube under argon was charged with 1-heptyne (450 μ L, 3.34 mmol) and THF (3.00 mL), and cooled to -70 $^{\circ}$ C. A solution of ⁿBuLi (1.90 mL of a 1.6 M solution in hexane, 3.00 mmol) was added dropwise and the mixture was stirred at -70 $^{\circ}$ C for 10 min. A Schlenk tube containing [Ru{(S)-PhGly}₂{(S)-BINAP}] (10.3 mg, 10.1 μ mol, 1.01 mol%) was evacuated and backfilled with argon. At 0 $^{\circ}$ C, MTBE (6.00 mL) and a portion of LiCCC₅H₁₁ solution (2.65 mL of a 0.56 M solution in THF, 1.50 mmol, 1.50 eq) were added, and the mixture was stirred for 30 min. Enone **131** (180 μ L, 1.00 mmol, 1.00 eq) was added dropwise and the reaction mixture was stirred at 0 $^{\circ}$ C for 3 h. 1 M HCl_(aq) (3 mL) was added, the layers were separated and the organic phase was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (pentane/Et₂O 9:1, 0.7 L) gave 1,2 addition product **133** (88.8 mg, 32 %) as a pale yellow oil, *R*_F (pentane/Et₂O 9:1) 0.30; **IR** (CHCl₃) 3524, 3065, 2962, 2933, 2874, 1723, 1600, 1494, 1449, 1370, 1177 cm⁻¹; ¹H **NMR** (400 MHz, CDCl₃) δ : 7.65-7.59 (m, 2H, Ar), 7.40-7.32 (m, 2H, Ar), 7.31-7.26 (m, 1H, Ar), 6.02 (dd, 1H, *J* = 15.3, 6.6 Hz, ⁱPrCH=CH), 5.64 (dd, 1H, *J* = 15.3, 1.3 Hz, ⁱPrCH=CH), 2.39-2.27 (m, 4H, 2 x CH₂), 1.64-1.54 (m, 2H, CH₂), 1.47-1.30 (m, 4H, CH₂, CH(CH₃)₂ and OH), 1.02 (dd, 6H, *J* = 6.7,

1.9 Hz, CH(CH₃)₂), 0.92 (t, 3H, *J* = 7.3 Hz, CH₂CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ: 144.6 (Ar), 137.3 (CH=CH), 131.5 (CH=CH), 128.1 (Ar), 127.5 (Ar), 125.7 (Ar), 88.1 (CC), 81.8 (CC), 72.9 (COH), 31.1 (CH₂), 30.3 (CH(CH₃)₂), 28.3 (CH₂), 22.2 (CH(CH₃)₂), 22.2 (CH₂), 18.8 (CH₂), 14.0 (CH₂CH₃); HRMS (ESI, pos.), *m/z* for C₁₉H₂₆O ([M + Na]⁺), calcd. 293.1881, found 293.1892.

3-isopropyl-1-phenyldec-4-yn-1-one **132**



A flame-dried, stirrer-equipped Schlenk tube under argon was charged with trimethylaluminium (750 µL of a 2.0 M solution in hexane, 1.50 mmol), MeN(SiMe₃)₂ (23.0 µL, 90.0 µmol) and 1-heptyne (240 µL, 1.80 mmol) and the reaction mixture was stirred at 25 °C for 16 h, before adding MTBE (2.00 mL). A Schlenk tube containing [Ru{(S)-PhGly}₂ {(S)-BINAP}] (10.3 mg, 10.1 µmol, 1.98 mol%) was evacuated and backfilled with argon. At 0 °C, MTBE (6.00 mL) and the Me₂AlCCC₅H₁₁ solution were added, and the mixture was stirred for 30 min. Enone **131** (90.0 µL, 509 µmol, 1.00 eq) was added dropwise and the reaction mixture was stirred at 0 °C for 3 h. 1 M HCl_(aq) (3 mL) was added, the layers were separated and the organic phase was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (pentane/Et₂O 30:1, 0.6 L) gave **132** (51.5 mg, 37 %) as a colourless oil, *R*_F (pentane/Et₂O 30:1) 0.20; IR (CHCl₃) 3367, 3063, 2959, 2931, 1688, 1598, 1449, 1265 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 8.01-7.95 (m, 2H, Ar), 7.60-7.54 (m, 1H, Ar), 7.50-7.44 (m, 2H, Ar), 3.27-3.16 (m, 1H, (CH₃)₂CH), 3.05-2.93 (m, 2H, CH₂CO), 2.10 (td, 2H, *J* = 7.1, 2.1 Hz, CCCH₂), 1.84-1.72 (m, 1H, (CH₃)₂CHCH), 1.47-1.36 (m, 2H, CH₂), 1.35-1.21 (m, 4H, 2 x CH₂), 1.04 (d, 3H, *J* = 6.7 Hz, CH(CH₃)_a(CH₃)_b), 1.00 (d, 3H, *J* = 6.7 Hz, CH(CH₃)_a(CH₃)_b), 0.87 (t, 3H, *J* = 7.0 Hz, CH₂CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ: 198.8 (CO), 137.3 (Ar), 132.9 (Ar), 128.5 (Ar), 128.2 (Ar),

82.9 (CC), 80.3 (CC), 42.1 (C(O)CH₂), 34.4 (CHCH(CH₃)₂), 31.4 (CH(CH₃)₂), 30.9 (CH₂), 28.7 (CH₂), 22.1 (CH₂), 21.2 ((C_aH₃)(C_bH₃)CH), 18.6 (CH₂), 18.0 ((C_aH₃)(C_bH₃)CH), 13.9 (CH₂CH₃); **HRMS** (ESI, pos.), *m/z* for C₁₉H₂₆O ([M + Na]⁺), calcd. 293.1881, found 293.1882.

3-isopropyl-1-phenyldec-4-yn-1-one **132**

A flame-dried, stirrer-equipped Schlenk tube under argon was charged with trimethylaluminium (1.50 mL of a 2.0 M solution in hexane, 3.00 mmol), MeN(SiMe₃)₂ (46.0 µL, 180 µmol) and 1-heptyne (480 µL, 3.60 mmol) and the reaction mixture was stirred at 25 °C for 16 h, before adding MTBE (4.00 mL). A Schlenk tube containing [Ru{(S)-PhGly}₂[(S)-BINAP]] (10.2 mg, 9.96 µmol, 1.00 mol%) was evacuated and backfilled with argon. At 0 °C, MTBE (6.00 mL) and a portion of Me₂AlCCC₅H₁₁ solution (2.60 mL, 1.50 mmol, 1.50 eq) were added, and the mixture was stirred for 30 min. Enone **131** (180 µL, 1.00 mmol, 1.00 eq) was added dropwise and the reaction mixture was stirred at 0 °C for 3 h. 1 M HCl_(aq) (3 mL) was added, the layers were separated and the organic phase was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (pentane/Et₂O 30:1, 0.88 L) gave **132** (71.5 mg, 26 %) as a pale yellow oil. Data as above.

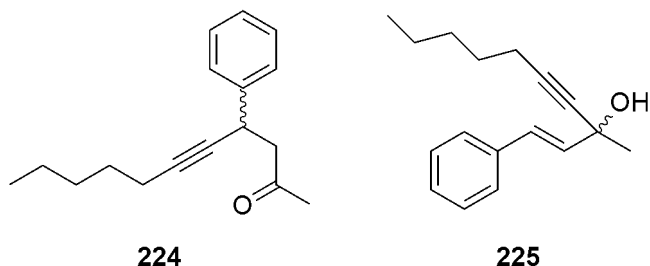
General Procedure 11: Racemic Conjugate Addition of Alkynylaluminium Reagents to Enones

A flame-dried, stirrer-equipped Schlenk tube under argon was charged with trimethylaluminium (3.00 mL of a 2.0 M solution in hexane, 6.00 mmol), MeN(SiMe₃)₂ (92.0 µL, 360 µmol) and alkyne (7.20 mmol) and the reaction mixture was stirred at 25 °C for 16 h, before adding MTBE (8.00 mL). In a separate Schlenk tube at 0 °C, MTBE (12.0 mL) and a portion of Me₂AlCCR solution (3.00 mmol, 3.00 eq) were stirred for 30 min. Enone (1.00 mmol, 1.00 eq) was added dropwise and the reaction mixture was stirred at 0 °C for 3 h. 1 M HCl_(aq) (6 mL) was added, the layers were separated and the organic phase was evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography.

(±)-3-isopropyl-1-phenyldec-4-yn-1-one 132

Using General Procedure **11**, 1-heptyne (950 μL , 7.20 mmol) giving $\text{Me}_2\text{AlCCC}_5\text{H}_{11}$ solution (5.40 mL, 3.00 mmol), and (*E*)-4-methyl-1-phenyl-2-penten-1-one **131** (180 μL , 1.00 mmol), eluting the column with pentane/ Et_2O 30:1 (0.6 L) gave (±)-**132** (270 mg, 98 %) as a colourless oil. Data as above.

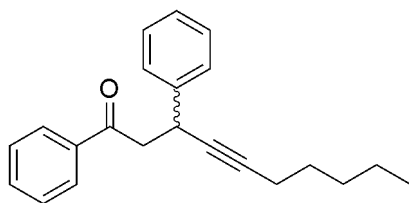
(±)-4-phenylundec-5-yn-2-one 224



Using General Procedure **11**, 1-heptyne (950 μL , 7.20 mmol) giving $\text{Me}_2\text{AlCCC}_5\text{H}_{11}$ solution (5.40 mL, 3.00 mmol), and benzylideneacetone (147 mg, 1.01 mmol, added as a solution in 1.00 mL MTBE), eluting the column with pentane/ Et_2O 4:1 (0.6 L) gave (±)-**224** (62.1 mg, 25 %) as a colourless oil, R_F (pentane/ Et_2O 4:1) 0.32; **IR** (CHCl_3) 3517, 3066, 2960, 2933, 2862, 1712, 1602, 1453, 1360, 1241, 1097, 934 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ : 7.42-7.36 (m, 2H, Ar), 7.35-7.29 (m, 2H, Ar), 7.26-7.20 (m, 1H, Ar), 4.20-4.13 (m, 1H, PhCH), 2.96-2.90 (m, 1H, $\text{PhCHCH}_a\text{H}_b$), 2.79-2.74 (m, 1H, $\text{PhCHCH}_a\text{H}_b$), 2.20 (td, 2H, $J = 7.1, 2.3$ Hz, CH_2), 2.15 (s, 3H, CH_3CO), 1.56-1.46 (m, 2H, CH_2), 1.42-1.26 (m, 4H, 2 x CH_2), 0.91 (t, 3H, $J = 7.0$ Hz, CH_3CH_2); **^{13}C NMR** (100.6 MHz, CDCl_3) δ : 206.2 (CO), 141.6 (Ar), 128.5 (Ar), 127.3 (Ar), 126.9 (Ar), 83.6 (CC), 80.5 (CC), 52.3 (COCH_2), 33.2 (PhCH), 31.0 (CH_2), 30.6 (COCH_3), 28.6 (CH_2), 22.2 (CH_2), 18.7 (CH_2), 14.0 (CH_2CH_3); **HRMS** (ESI, pos.), m/z for $\text{C}_{17}\text{H}_{22}\text{O}$ ($[\text{M} + \text{Na}]^+$), calcd. 265.1568, found 265.1561; and 1,2-addition product (±)-**225** (92.2 mg, 38 %) as a colourless oil, R_F (pentane/ Et_2O 4:1) 0.33; **IR** (CHCl_3) 3594, 3011, 2959, 2934, 2862, 1450, 1330, 1193, 1072, 970, 929 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ : 7.45-7.39 (m, 2H, Ar), 7.36-7.30 (m, 2H, Ar), 7.29-7.23 (m, 1H, Ar), 6.87 (d, 1H, $J = 15.8$ Hz, $\text{PhCH}=\text{CH}$), 6.32 (d, 1H, $J = 15.8$ Hz, $\text{PhCH}=\text{CH}$), 2.28 (t,

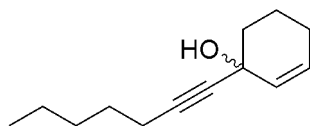
2H, $J = 7.2$ Hz, CCCH_2), 2.10 (br s, 1H, OH), 1.64 (s, 3H, CH_3COH), 1.62-1.53 (m, 2H, CH_2), 1.47-1.30 (m, 4H, 2 x CH_2), 0.93 (t, 3H, $J = 7.3$ Hz, CH_2CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 136.4 (Ar), 134.0 ($\text{PhCH}=\text{CH}$), 128.7 ($\text{PhCH}=\text{CH}$), 128.6 (Ar), 127.8 (Ar), 126.7 (Ar), 85.9 (CC), 82.3 (CC), 68.2 (COH), 31.1 (CH_2), 30.8 (CH_3COH), 28.4 (CH_2), 22.2 (CH_2), 18.7 (CH_2), 14.0 (CH_2CH_3); HRMS (ESI, pos.), m/z for $\text{C}_{17}\text{H}_{22}\text{O}$ ($[\text{M} + \text{Na}]^+$), calcd. 265.1568, found 265.1551.

(±)-1,3-diphenyldec-4-yn-1-one 226



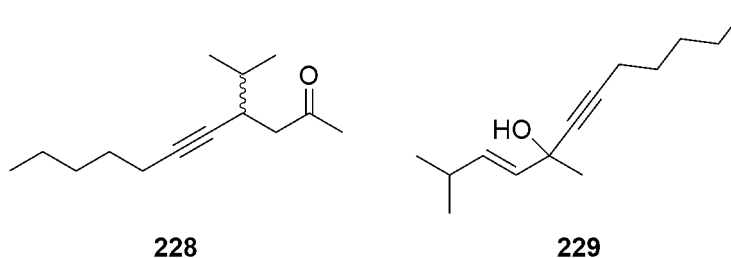
Using General Procedure **11**, 1-heptyne (950 μL , 7.20 mmol) giving $\text{Me}_2\text{AlCCC}_5\text{H}_{11}$ solution (5.75 mL, 3.00 mmol), and chalcone (208 mg, 1.00 mmol, added as a solution in 1.00 mL MTBE), eluting the column with pentane/ Et_2O 9:1 (0.9 L) gave (±)-**226** (216 mg, 71 %) as a colourless oil, R_F (pentane/ Et_2O 9:1) 0.48; IR (CHCl_3) 3515, 3066, 3007, 2959, 2933, 2861, 1687, 1599, 1494, 1450, 1352, 1256, 1182, 977 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.99-7.92 (m, 2H, Ar), 7.59-7.53 (m, 1H, Ar), 7.50-7.42 (m, 4H, Ar), 7.38-7.30 (m, 2H, Ar), 7.27-7.21 (m, 1H, Ar), 4.45-4.38 (m, 1H, PhCH), 3.55 (dd, 1H, $J = 16.4, 8.3$ Hz, $\text{CH}_a\text{H}_b\text{CO}$), 3.28 (dd, 1H, $J = 16.4, 6.0$ Hz, $\text{CH}_a\text{H}_b\text{CO}$), 2.16 (td, 2H, $J = 7.1, 2.1$ Hz, CCCH_2), 1.51-1.42 (m, 2H, CH_2), 1.37-1.22 (m, 4H, 2 x CH_2), 0.87 (t, 3H, $J = 7.0$ Hz, CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 197.5 (CO), 142.0 (Ar), 137.0 (Ar), 133.1 (Ar), 128.5 (2, Ar), 128.2 (Ar), 127.5 (Ar), 126.8 (Ar), 83.6 (CC), 80.9 (CC), 47.6 (COCH_2), 33.3 (PhCH), 31.0 (CH_2), 28.5 (CH_2), 22.1 (CH_2), 18.7 (CH_2), 13.9 (CH_3); HRMS (ESI, pos.), m/z for $\text{C}_{22}\text{H}_{24}\text{O}$ ($[\text{M} + \text{Na}]^+$), calcd. 327.1725, found 327.1701.

(±)-1-(hept-1-ynyl)cyclohex-2-enol 227



Using General Procedure **11**, 1-heptyne (950 μ L, 7.20 mmol) giving $\text{Me}_2\text{AlCCC}_5\text{H}_{11}$ solution (5.75 mL, 3.00 mmol), and cyclohexenone (97.0 μ L, 1.00 mmol), eluting the column with pentane/ Et_2O 2:1 (0.6 L) gave 1,2-addition product **(±)-227** (130 mg, 67 %) as a colourless oil, R_F (pentane/ Et_2O 2:1) 0.54; **IR** (CHCl_3) 3595, 3006, 2934, 2863, 1456, 1328, 1241, 1073, 1038, 956 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 5.80 (dt, 1H, $J = 9.9, 3.5$ Hz, $\text{CH}_2\text{CH}=\text{CH}$), 5.74 (dt, 1H, $J = 9.9, 1.8$ Hz, $\text{CH}_2\text{CH}=\text{CH}$), 2.20 (t, 2H, $J = 7.2$ Hz, CH_2), 2.06-1.95 (m, 4H, 2 x CH_2), 1.93-1.85 (m, 1H, OH), 1.82-1.69 (m, 2H, CH_2), 1.56-1.46 (m, 2H, CH_2), 1.40-1.26 (m, 4H, 2 x CH_2), 0.90 (t, 3H, $J = 7.0$ Hz, CH_3); $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ : 131.1 ($\text{CH}=\text{CH}$), 129.1 ($\text{CH}=\text{CH}$), 84.4 (CC), 83.8 (CC), 65.2 (COH), 38.2 (CH_2 in ring), 31.0 (CH_2 in chain), 28.3 (CH_2 in chain), 24.7 (CH_2 in ring), 22.1 (CH_2 in chain), 19.2 (CH_2 in ring), 18.7 (CH_2 in chain), 13.9 (CH_3); **HRMS** (ESI, pos.), m/z for $\text{C}_{13}\text{H}_{20}\text{O}$ ($[\text{M} + \text{Na}]^+$), calcd. 215.1412, found 215.1398.

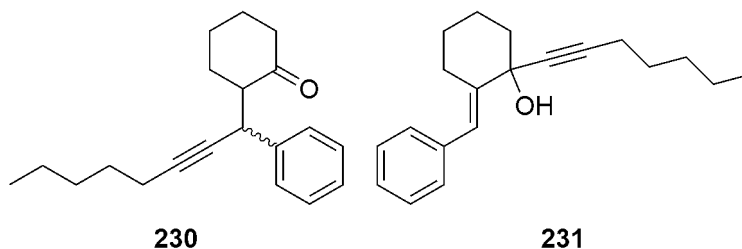
(±)-4-isopropylundec-5-yn-2-one 228



Using General Procedure **11**, 1-heptyne (950 μ L, 7.20 mmol) giving $\text{Me}_2\text{AlCCC}_5\text{H}_{11}$ solution (5.70 mL, 3.00 mmol), and (*E*)-5-methylhex-3-en-2-one (132 μ L, 1.00 mmol), eluting the column with pentane/ Et_2O 9:1 (1.0 L) gave **(±)-228** (61.0 mg, 29 %) as a colourless oil, R_F (pentane/ Et_2O 9:1) 0.27; **IR** (CHCl_3) 3587, 2963, 2933, 2874, 2210, 1714, 1466, 1359, 1251, 1164 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 2.79-2.72 (m, 1H, $(\text{CH}_3)_2\text{CHCH}$), 2.62-2.56 (m, 1H, $\text{CH}_a\text{H}_b\text{CO}$), 2.47-2.41 (m, 1H, $\text{CH}_a\text{H}_b\text{CO}$), 2.19 (s, 3H, CH_3CO), 2.13 (td, 2H, $J = 7.0, 2.0$ Hz, CCCH_2), 1.73-1.60 (m, 1H, $(\text{CH}_3)_2\text{CH}$), 1.53-1.41 (m, 2H, CH_2), 1.40-1.24 (m, 4H, 2 x CH_2),

0.98 (d, 3H, $J = 6.6$ Hz, CH_2CH_3), 0.95-0.85 (m, 6H, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 207.7 (CO), 82.9 (CC), 80.1 (CC), 47.2 ($\text{C}(\text{O})\text{CH}_2$), 34.2 ($\text{CHCH}(\text{CH}_3)_2$), 31.5 ($\text{CH}(\text{CH}_3)_2$), 31.0 (CH_2), 30.5 (COCH_3), 28.7 (CH_2), 22.1 (CH_2), 20.9 ($((\text{C}_a\text{H}_3)(\text{C}_b\text{H}_3)\text{CH})$), 18.6 (CH_2), 18.1 ($((\text{C}_a\text{H}_3)(\text{C}_b\text{H}_3)\text{CH})$), 14.0 (CH_2CH_3); **HRMS** (ESI, pos.), m/z for $\text{C}_{14}\text{H}_{24}\text{O}$ ($[\text{M} + \text{Na}]^+$), calcd. 231.1725, found 231.1713; and 1,2-addition product (\pm)-**229** (64.5 mg, 31 %) as a colourless oil, R_F (pentane/ Et_2O 9:1) 0.24; **IR** (CHCl_3) 3593, 2961, 2933, 2871, 1466, 1329, 1071, 975 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 5.92 (dd, 1H, $J = 15.5, 6.6$ Hz, $\text{CH}=\text{CH}$), 5.53 (dd, 1H, $J = 15.5, 1.4$ Hz, $\text{CH}=\text{CH}$), 2.36-2.26 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.22 (t, 2H, $J = 7.0$ Hz, CCCH_2), 1.98 (br s, 1H, OH), 1.52 (s, 3H, CH_3COH), 1.44-1.23 (m, 6H, 3 x CH_2), 1.01 (d, 6H, $J = 6.9$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.90 (t, 3H, $J = 7.3$ Hz, CH_2CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 136.9 ($\text{CH}=\text{CH}$), 131.7 ($\text{CH}=\text{CH}$), 85.2 (CC), 82.8 (CC), 68.0 (COH), 31.0 (CH_2), 30.8 (CH_3COH), 30.3 ($\text{CH}(\text{CH}_3)_2$), 28.4 (CH_2), 22.2 (CH_2), 22.2 (d, $\text{CH}(\text{CH}_3)_2$), 18.6 (CH_2), 14.0 (CH_2CH_3); **HRMS** (ESI, pos.), m/z for $\text{C}_{14}\text{H}_{24}\text{O}$ ($[\text{M} + \text{Na}]^+$), calcd. 231.1725, found 231.1717.

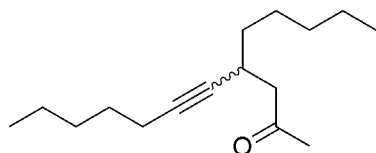
(\pm)-2-(1-phenyloct-2-ynyl)cyclohexanone 230



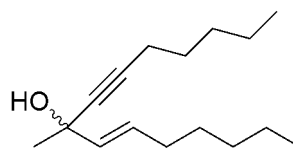
Using General Procedure **11**, 1-heptyne (950 μL , 7.20 mmol) giving $\text{Me}_2\text{AlCCC}_5\text{H}_{11}$ solution (5.70 mL, 3.00 mmol), and 2-benzylidenecyclohexanone (186 mg, 1.00 mmol, added as a solution in 1.00 mL MTBE), eluting the column with pentane/ Et_2O 9:1 (1.0 L) gave (\pm)-**230** (18.7 mg, 7 %) as a colourless oil, R_F (pentane/ Et_2O 9:1) 0.37; **IR** (CHCl_3) 3692, 3518, 2933, 2862, 1749, 1710, 1602, 1450, 1242, 1177, 1129 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.40-7.34 (m, 2H, Ar), 7.33-7.26 (m, 2H, Ar), 7.25-7.19 (m, 1H, Ar), 4.13 (dt, 1H, $J = 7.2, 2.3$ Hz, CHCO), 2.78-2.70 (m, 1H, PhCH), 2.49-2.41 (m, 1H, $\text{COCHCH}_a\text{H}_b$), 2.39-2.29 (m, 1H, $\text{COCHCH}_a\text{H}_b$), 2.18 (td, 2H, $J = 7.1, 2.3$ Hz, CCCH_2), 1.86-1.76 (m, 2H, CH_2), 1.71-1.43 (m, 4H, 2 x CH_2), 1.40-1.19 (m, 6H, 3 x CH_2), 0.89 (td, 3H, $J = 7.1$,

1.9 Hz, CH₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 210.7 (CO), 139.9 (Ar), 128.8 (Ar), 128.1 (Ar), 126.7 (Ar), 82.8 (CC), 81.3 (CC), 57.6 (COCH), 42.0 (COCH₂), 36.6 (COCHCH₂), 31.0 (CH₂), 30.9 (PhCH), 28.6 (CH₂ in chain), 27.8 (CH₂), 24.4 (CH₂), 22.2 (CH₂ in chain), 18.8 (CH₂ in chain), 14.0 (CH₃); **HRMS** (ESI, pos.), *m/z* for C₂₀H₂₆O ([M + Na]⁺), calcd. 305.1881, found 305.1870; and 1,2-addition product (±)-**231** (192 mg, 68 %) as a viscous, colourless oil, **R_F** (pentane/Et₂O 9:1) 0.22; **IR** (CHCl₃) 3593, 2936, 2861, 1600, 1495, 1446, 1319, 1241, 1073 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 7.40-7.29 (m, 2H, Ar), 7.29-7.19 (m, 3H, Ar), 6.90 (s, 1H, PhCH), 2.72-2.62 (m, 1H, COHCH_aH_b), 2.47-2.38 (m, 1H, COHCH_aH_b), 2.28 (t, 2H, *J* = 7.1 Hz, CCCH₂), 2.09 (br s, 1H, OH), 2.07-1.69 (m, 4H, 2 x CH₂), 1.65-1.28 (m, 8H, 4 x CH₂), 0.92 (t, 3H, *J* = 7.2 Hz, CH₂CH₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 143.8 (C=CHPh), 137.8 (Ar), 129.0 (Ar), 128.0 (Ar), 126.3 (Ar), 121.4 (C=CHPh), 86.6 (CC), 82.5 (CC), 71.7 (COH), 42.7 (CH₂ in ring), 31.1 (CH₂ in chain), 28.4 (CH₂ in chain), 27.3 (CH₂ in ring), 26.2 (CH₂ in ring), 23.1 (CH₂ in ring), 22.2 (CH₂ in chain), 18.7 (CH₂ in chain), 14.0 (CH₃); **HRMS** (ESI, pos.), *m/z* for C₂₀H₂₆O ([M + Na]⁺), calcd. 305.1881, found 305.1862.

(±)-4-pentylundec-5-yn-2-one 232



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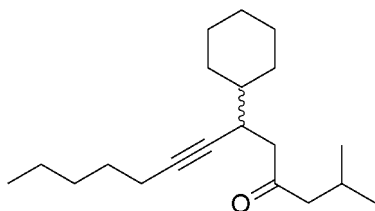


233

Using General Procedure **11**, 1-heptyne (950 μL, 7.20 mmol) giving Me₂AlCCC₅H₁₁ solution (5.75 mL, 3.00 mmol), and 3-nonen-2-one (165 μL, 1.00 mmol), eluting the column with pentane/Et₂O 9:1 (0.9 L) gave (±)-**232** (71.3 mg, 30 %) as a colourless oil, **R_F** (pentane/Et₂O 9:1) 0.38; **IR** (CHCl₃) 3402, 3007, 2959, 2932, 2860, 1713, 1467, 1362, 1242, 1163 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 2.85-2.75 (m, 1H, CCCH), 2.63-2.56 (m, 1H, CH₃COCH_aH_b), 2.49-2.44 (m, 1H, CH₃COCH_aH_b), 2.18 (s, 3H, CH₃CO), 2.13 (td, 2H, *J* = 7.0, 2.2 Hz, CCCH₂), 1.55-1.20 (m, 14H, 7 x CH₂), 0.89 (t, 3H, *J* = 7.6 Hz, CH₂CH₃), overlapped with 0.89 (t, 3H, *J* = 7.6 Hz, CH₂CH₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 207.4 (CO), 82.1 (CC), 81.9 (CC), 49.5

(COCH₂), 35.2 (CH), 31.5 (CH₂), 31.0 (CH₂), 30.5 (COCH₃), 28.7 (CH₂), 27.4 (CH₂), 26.9 (CH₂), 22.6 (CH₂), 22.2 (CH₂), 18.6 (CH₂), 14.0 (CH₂CH₃), 14.0 (CH₂CH₃); **HRMS** (ESI, pos.), *m/z* for C₁₆H₂₈O ([M + Na]⁺), calcd. 259.2038, found 259.2029; and 1,2-addition product (±)-**233** (78.4 mg, 33 %), **R_F** (pentane/Et₂O 9:1) 0.21; **IR** (CHCl₃) 3516, 2960, 2933, 2862, 1717, 1601, 1467, 1379, 1250, 1109 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 5.93 (dt, 1H, *J* = 15.3, 6.8 Hz, CH=CHCH₂), 5.56 (dt, 1H, *J* = 15.3, 1.5 Hz, CH=CHCH₂), 2.21 (t, 2H, *J* = 7.2 Hz, CCCH₂), 2.10 (s, 1H, OH), 2.05-2.00 (m, 2H, CH=CHCH₂), 1.56-1.44 (m, 3H, CH₃COH), 1.43-1.22 (m, 12H, 6 x CH₂), 0.92-0.84 (m, 6H, 2 x CH₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 134.5 (CH=CH), 130.1 (CH=CH), 85.0 (CC), 82.8 (CC), 67.9 (COH), 31.7 (CH₂), 31.4 (CH₂), 31.0 (CH₂), 30.7 (CH₃COH), 28.7 (CH₂), 28.3 (CH₂), 22.5 (CH₂), 22.1 (CH₂), 18.6 (CH₂), 13.9 (CH₂CH₃), 13.9 (CH₂CH₃); **HRMS** (ESI, pos.), *m/z* for C₁₆H₂₈O ([M + Na]⁺), calcd. 259.2038, found 259.2024.

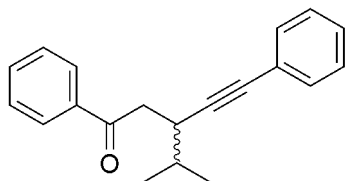
(±)-6-cyclohexyl-2-methyltridec-7-yn-4-one 234



Using General Procedure **11**, 1-heptyne (950 μL, 7.20 mmol) giving Me₂AlCCC₅H₁₁ solution (5.75 mL, 3.00 mmol), and (*E*)-1-cyclohexyl-5-methyl-1-hexen-3-one (194 mg, 1.00 mmol, added as a solution in 1.00 mL MTBE), eluting the column with pentane/Et₂O 9:1 (1.0 L) gave (±)-**234** (66.8 mg, 23 %) as a colourless oil, **R_F** (pentane/Et₂O 9:1) 0.45; **IR** (CHCl₃) 2959, 2930, 2856, 1709, 1467, 1450, 1368, 1193 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 2.79-2.72 (m, 1H, CCCH), 2.59-2.53 (m, 1H, COCH_aH_b), 2.45-2.39 (m, 1H, COCH_aH_b), 2.33 (dd, 2H, *J* = 6.9, 3.1 Hz, COCH₂ⁱPr), 2.20-2.15 (m, 1H, CH), 2.13 (td, 2H, *J* = 7.0, 2.1 Hz, CCCH₂), 1.80-1.70 (m, 3H, CH₂ and CH), 1.69-1.61 (m, 2H, CH₂), 1.51-1.42 (m, 2H, CH₂), 1.40-1.06 (m, 10H, 5 x CH₂), 0.94-0.87 (m, 9H, 3 x CH₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 209.5 (CO), 82.6 (CC), 80.9 (CC), 52.5 (COCH₂R), 46.4 (COCH₂R'), 41.3 (CH in ring), 33.3 (CCCH), 31.3 (CH(CH₃)₂), 31.0 (CH₂), 28.9 (CH₂), 28.8

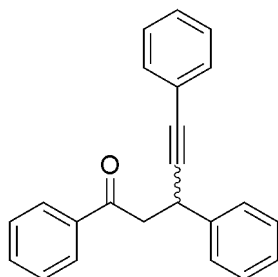
(CH₂), 26.4 (CH₂), 26.2 (CH₂), 24.4 (CH₂), 22.6 (d, CH(CH₃)₂), 22.2 (CH₂), 18.7 (CH₂), 14.0 (CH₂CH₃); **HRMS** (ESI, pos.), *m/z* for C₂₀H₃₄O ([M + Na]⁺), calcd. 313.2507, found 313.2487.

(±)-3-isopropyl-1,5-diphenylpent-4-yn-1-one 235



Using General Procedure **11**, phenylacetylene (790 μ L, 7.20 mmol) giving Me₂AlCCPh solution (5.75 mL, 3.00 mmol), and (*E*)-4-methyl-1-phenyl-2-penten-1-one (180 μ L, 1.00 mmol), eluting the column with pentane/Et₂O 19:1 (0.6 L, solid load) gave (±)-**235** (276 mg, 100 %) as white needles, **mp** 66-68 °C; **R_F** (pentane/Et₂O 19:1) 0.23; **IR** (CHCl₃) 2964, 2929, 2874, 1686, 1598, 1581, 1490, 1449, 1358, 1269, 1181, 986 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ : 8.06-7.99 (m, 2H, Ar), 7.61-7.56 (m, 1H, Ar), 7.53-7.46 (m, 2H, Ar), 7.37-7.30 (m, 2H, Ar), 7.29-7.22 (m, 3H, Ar), 3.41-3.33 (m, 1H, PhCOCH_aH_b), 3.32-3.26 (m, 1H, PhCCCH), 3.16-3.08 (m, 1H, PhCOCH_aH_b), 1.99-1.86 (m, 1H, CH(CH₃)₂), 1.14 (d, 3H, *J* = 6.7 Hz, CH(C_aH₃)(C_bH₃)), 1.10 (d, 3H, *J* = 6.7 Hz, CH(C_aH₃)(C_bH₃)); **¹³C NMR** (100.6 MHz, CDCl₃) δ : 198.4 (CO), 137.1 (Ar), 133.1 (Ar), 131.5 (Ar), 128.6 (Ar), 128.2 (Ar), 128.1 (Ar), 127.5 (Ar), 123.8 (Ar), 90.6 (CC), 83.0 (CC), 41.7 (C(O)CH₂), 34.7 (CHCH(CH₃)₂), 31.4 (CH(CH₃)₂), 21.3 ((C_aH₃)(C_bH₃)CH), 18.1 ((C_aH₃)(C_bH₃)CH); **HRMS** (ESI, pos.), *m/z* for C₂₀H₂₀O ([M + Na]⁺), calcd. 299.1412, found 299.1418.

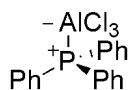
(±)-1,3,5-triphenylpent-4-yn-1-one **236**



Using General Procedure **11**, phenylacetylene (790 μ L, 7.20 mmol) giving Me_2AlCCPh solution (5.75 mL, 3.00 mmol), and chalcone (210 mg, 1.01 mmol, added as a solution in 1.00 mL MTBE), eluting the column with pentane/ Et_2O 9:1 (1.3 L, solid load) gave (±)-**236** (120 mg, 38 %) as a white solid, **mp** 85-88 $^\circ\text{C}$; **R_F** (pentane/ Et_2O 9:1) 0.28; **IR** (CHCl_3) 3692, 3068, 3006, 1687, 1599, 1491, 1449, 1351, 1260, 1183, 971 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ : 8.01-7.95 (m, 2H, Ar), 7.60-7.51 (m, 3H, Ar), 7.50-7.43 (m, 2H, Ar), 7.40-7.33 (m, 4H, Ar), 7.30-7.24 (m, 4H, Ar), 4.68-4.64 (m, 1H, PhCH), 3.71-3.65 (m, 1H, $\text{PhCOCH}_a\text{H}_b$), 3.46-3.40 (m, 1H, $\text{PhCOCH}_a\text{H}_b$); **^{13}C NMR** (100.6 MHz, CDCl_3) δ : 197.1 (CO), 141.2 (Ar), 136.9 (Ar), 133.2 (Ar), 131.6 (Ar), 128.7 (Ar), 128.6 (Ar), 128.2 (Ar), 128.1 (Ar), 127.9 (Ar), 127.6 (Ar), 127.1 (Ar), 123.4 (Ar), 90.7 (CC), 83.3 (CC), 47.3 (CH_2), 33.7 (PhCH); **HRMS** (ESI, pos.), m/z for $\text{C}_{23}\text{H}_{18}\text{O}$ ($[\text{M} + \text{Na}]^+$), calcd. 333.1255, found 333.1240.

5.3.4.3 Friedel-Crafts Alkylation of Arylphosphines

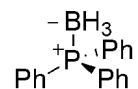
Triphenylphosphine aluminium chloride complex **139**



Triphenylphosphine (525 mg, 2.00 mmol, 1.00 eq) was dissolved in Et_2O (2.00 mL) and added slowly to a solution of AlCl_3 (267 mg, 2.00 mmol, 1.00 eq) in Et_2O (2.00 mL). The reaction mixture was stirred for 10 min to redissolve the initially formed precipitate. The ether was allowed to evaporate at room temperature and any residual solvent was removed in a dessicator evacuated by filter pump to give the product **139** (851 mg, 69 %, *ca.* 3.0 eq Et_2O) as a viscous pale yellow oil with a solid white crust, **^1H NMR** (400 MHz, CDCl_3) δ : 7.58-7.40 (m, 15H, Ar); **^{13}C NMR** (100.6 MHz, CDCl_3) δ : 133.9

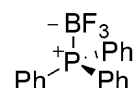
(Ar), 133.8 (Ar), 131.2 (Ar), 129.3 (d, Ar); ^{31}P NMR (162.0 MHz, CDCl_3) δ : -0.14. Spectroscopic data consistent with those in the literature.¹⁵⁷

Triphenylphosphine – borane **140**



Triphenylphosphine (5.25 g, 20.0 mmol, 1.00 eq) was dissolved in dry THF (20.0 mL) under argon and NaBH_4 (1.15 g, 30.4 mmol, 1.52 eq) was added in one portion at 0 °C. A solution of glacial acetic acid (1.95 mL, 34.0 mmol, 1.70 eq) in THF (8.00 mL) was added dropwise over 30 min, then cooling was removed and the reaction mixture was stirred at room temperature for 1h. Water (10 mL) and acetic acid (5 mL) were added and the resulting biphasic mixture was filtered by suction filtration to give the phosphine borane **140** (5.25 g, 95 %) as a white crystalline solid, ^1H NMR (400 MHz, CDCl_3) δ : 7.64-7.55 (m, 6H, Ar), 7.55-7.48 (m, 3H, Ar), 7.48-7.41 (m, 6H, Ar), 1.55-0.72 (br m, 3H, BH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 133.2 (d, Ar), 131.2 (Ar), 129.4 (Ar), 128.8 (d, Ar); ^{31}P NMR (162.0 MHz, CDCl_3) δ : 20.63 (br m). Spectroscopic data consistent with those in the literature.¹⁵⁸

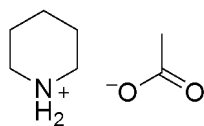
Triphenylphosphine – boron trifluoride **141**



Triphenylphosphine (5.26 g, 20.1 mmol, 1.00 eq) was dissolved in dry Et_2O (20.0 mL) under argon and $\text{BF}_3\cdot\text{OEt}_2$ (2.45 mL, 20.0 mmol, 1.00 eq) was added slowly. The white precipitate was filtered off and dried to give the first crop of product **141** (275 mg, 4 %) as a white crystalline solid. The filtrate was evaporated under reduced pressure to give a second crop of product **141** (6.25 g, 95 %) as a white crystalline solid, ^1H NMR (400 MHz, CDCl_3) δ : 7.83-7.72 (m, 9H, Ar), 7.70-7.60 (m, 6H, Ar); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 135.3 (Ar), 134.0 (Ar), 133.9 (Ar), 130.5 (Ar), 130.4 (Ar); ^{31}P NMR (162.0 MHz, CDCl_3) δ : 3.47 (br s); ^{19}F NMR (376.5 MHz, CDCl_3) δ : -150.16 (s). Spectroscopic data consistent with those reported in the literature.¹⁵⁹

5.3.4.4 Organocatalytic Preparation of (*E*)-5-methylhex-3-en-2-one

Piperidinium acetate **142**



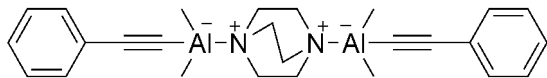
A solution of acetic acid (630 μ L, 11.0 mmol, 1.10 eq) in Et₂O (10.0 mL) was added slowly to a solution of piperidine (1.00 mL, 10.0 mmol, 1.00 eq) in Et₂O (20.0 mL) at 0 °C. The mixture was stirred for 1 h, then allowed to come to room temperature. The precipitate was filtered off by cannula filtration, washed with Et₂O (3 x 10 mL) and pentane (3 x 10 mL), and dried under high vacuum for 1 h to give an off-white solid (1.24 g, 85 %), which was used directly in enone synthesis reactions.

(*E*)-5-methylhex-3-en-2-one **114**

Between ten sealed tubes, piperidinium acetate (1.42 g, 9.75 mmol, 20.0 mol%) was added to a solution of isobutyraldehyde (4.60 mL, 50.4 mmol, 1.00 eq) in acetone (50.0 mL). The reaction mixture was stirred at 75 °C for 90 h. At room temperature, the tubes were combined, saturated NaHCO_{3(aq)} (50 mL) and Et₂O (50 mL) were added, the layers were separated and the aqueous phase was extracted with Et₂O (3 x 25 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure to give the crude product. Proton NMR spectroscopy showed a *ca.* 2:4:1 mixture of desired product **114**, isomer **143** and aldol product **144**. The crude mixture (2.55 g, 1.00 eq) was dissolved in CH₂Cl₂ (14.0 mL) and *m*CPBA (2.93 g, 80 wt%, 13.6 mmol, 1.10 eq w.r.t. isomer **143**) was added at 0 °C. The solution was stirred for 30 min. A solution of sodium sulfite (3.02 g) in H₂O (15.0 mL) was added and the mixture stirred for a further 5 min. Saturated NaHCO_{3(aq)} (10 mL) was added and the layers were separated. The organic phase was dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (pentane/Et₂O 4:1, 0.8 L) gave desired product **114** (347 mg, 6 %) as a pale yellow oil. Data as for general procedure **6**.

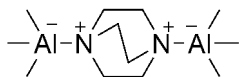
5.3.5 Alkynyl DABAL-Me₃ Analogues

Bis(dimethyl(phenylethynyl)aluminium)-1,4-diazabicyclo[2.2.2]-octane 145



A flame-dried, stirrer-equipped Schlenk tube under argon was charged with trimethylaluminium (4.50 mL of a 2.0 M solution in hexane, 9.00 mmol, 1.00 eq), MeN(SiMe₃)₂ (140 μ L, 540 μ mol, 6.00 mol%) and phenylacetylene (1.20 mL, 10.8 mmol, 1.20 eq) and the reaction mixture was stirred at 40 °C for 5 h. The reaction mixture was allowed to cool to room temperature and a solution of DABCO (507 mg, 4.52 mmol, 50.2 mol%) in toluene (4.50 mL) was added. The solution was stirred at room temperature for 30 min before the solvent was removed *in vacuo* to give a mixture of desired and polymeric products as a white solid, which was used as obtained.

Bis(trimethylaluminium)-1,4-diazabicyclo[2.2.2]-octane (DABAL-Me₃) 219



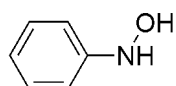
Neat trimethylaluminium (3.00 mL, 31.3 mmol) was added to a solution of freshly sublimed DABCO (1.70 g, 15.2 mmol) in toluene (15.0 mL) at 0 °C under argon. The resulting white precipitate was allowed to settle and the supernatant toluene was removed by cannula. Dry Et₂O (10.0 mL) was added and swirled with the solid, before allowing to settle and removal of the supernatant by cannula. Et₂O washing was repeated four times before the residual slurry was evaporated to dryness under high vacuum to afford the product (3.70 g, 95 %) as a white solid, ¹H NMR (400 MHz, C₆D₆) δ : 2.02 (s, 12H, 6 x CH₂), -0.61 (s, 18H, 6 x CH₃); ¹³C NMR (100.6 MHz, C₆D₆) δ : 44.4 (NCH₂), Al-CH₃ not observed. Data were consistent with those in the literature.¹³⁴

Bis(dimethyl(phenylethynyl)aluminium)-1,4-diazabicyclo[2.2.2]-octane 145

A flame-dried, stirrer-equipped Schlenk tube under argon was charged with DABAL-Me₃ **219** (257 mg, 1.00 mmol, 1.00 eq) and toluene (10.0 mL). Phenylacetylene (220 μ L, 2.00 mmol, 2.00 eq) was added and the reaction mixture was heated to reflux before allowing to cool to room temperature over 14.5 h. The solution was cooled at 4 °C for 25.5 h and then cooled at -18 °C for 23.5 h, giving small granular crystals. The mixture was allowed to come to room temperature, filtered by cannula filtration and the solvent was removed under high vacuum, to give white granules of insufficient size for X-ray crystallography.

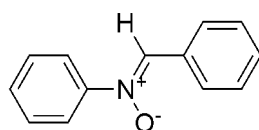
5.3.6 Use of Organoaluminium Reagents in the Kinugasa Reaction

General Procedure 12: Purification of *N*-Phenylhydroxylamine



Commercial *N*-phenylhydroxylamine (1.00 g) was dissolved in benzene (40.0 mL), filtered to remove NaCl impurities, and petrol (40.0 mL) was added to give rapid crystallisation. Filtration gave the hydroxylamine (458 mg) as a fluffy white crystalline solid.

N*, α -Diphenylnitron **150*



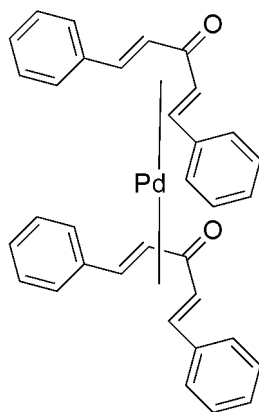
Purified *N*-phenylhydroxylamine (458 mg, 4.20 mmol, 1.00 eq) was mixed with EtOH (2.00 mL) and the mixture was briefly warmed to 40-60 °C with swirling. Distilled benzaldehyde (430 μ L, 4.20 mmol, 1.00 eq) was added, the flask stoppered, and the reaction mixture was stirred in the dark at room temperature for 16 h. The resulting solid was collected on a sinter funnel and washed with EtOH (10 mL), giving off-white needles. The product was redissolved in the minimum amount of EtOH and kept in the freezer overnight. The solution was evaporated under reduced pressure to give **150** (297 mg,

36 %) as off-white sheets. The sinter funnel was flushed with CH_2Cl_2 (10 mL) and the solution was evaporated under reduced pressure. The residue was dissolved in the minimum amount of EtOH and kept in the freezer overnight. The resulting solid was filtered off to give a second crop of **150** (117 mg, 14 %) as white needles, $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.45-8.38 (m, 2H, Ar), 7.94 (s, 1H, PhCH), 7.82-7.77 (m, 2H, Ar), 7.54-7.44 (m, 6H, Ar); $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ : 149.1 (Ar), 134.6 (PhCH), 130.9 (Ar), 130.6 (Ar), 129.9 (Ar), 129.1 (Ar), 129.0 (Ar), 128.6 (Ar), 121.7 (Ar). Data were consistent with those in the literature.⁷⁶

5.4 Pd-catalysed Cross-Coupling of Alkynylaluminium Reagents

5.4.1 Cross-Coupling to Aryl Halides

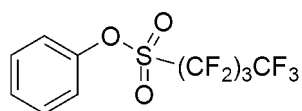
Bis(dibenzylideneacetone)palladium(0) $\text{Pd}(\text{dba})_2$ **185**



Acetone (950 μL , 13.0 mmol, 1.00 eq) was added to benzaldehyde (2.66 g, 25.1 mmol, 1.93 eq). Solid NaOH (2.50 g) was dissolved in H_2O (25.0 mL) and ethanol (20.0 mL) was added. This solution was added to the acetone/benzaldehyde mixture and the reaction mixture was stirred at 20-25 $^\circ\text{C}$ for 15 min. The resultant yellow precipitate was filtered off by suction, washing with H_2O (3 x 20 mL) to give the crude product. The crude product was recrystallised (EtOAc), dried (MgSO_4) after hot filtration, and the solvent was evaporated under reduced pressure to give **184** (2.24 g, 73 %) as a bright yellow crystalline solid. Solid PdCl_2 (444 mg, 2.50 mmol, 1.00 eq) and NaCl (146 mg, 2.51 mmol, 1.00 eq) were dissolved in MeOH (12.5 mL) and stirred at room temperature for 17 h. The resulting dark brown solution was filtered

through a plug of cotton wool and diluted to 75 mL with MeOH. The solution was heated to 60 °C and dibenzylideneacetone (1.75 g, 7.49 mmol, 3.00 eq) was added to the stirred solution. Stirring was continued for 15 min before addition of anhydrous NaOAc (3.76 g). The reaction mixture was immediately removed from the heat and stirring was continued under argon for 1 h until cooled to room temperature. The reaction mixture was cooled in an ice-bath for 10 min to ensure complete precipitation, and the precipitate was filtered off and washed with MeOH (5 x 1.3 mL), H₂O (5 x 2.5 mL) and acetone (5 x 1 mL). When air-dry, the product was dried under high vacuum for 1 h to yield **185** (1.33 g, 92 %) as a dark purple/brown powder, **mp** 145-147 °C (lit.¹⁶⁰ mp 150 °C), which was used as obtained.

Phenyl nonaflate **186**

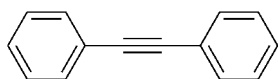


A solution of ⁿBuLi (3.45 mL of a 1.6 M solution in hexane, 5.50 mmol, 1.10 eq) was added to a solution of phenol (469 mg, 4.99 mmol, 1.00 eq) in THF (17.0 mL) at 0 °C under argon. The reaction mixture was stirred at this temperature for 10 min before a solution of nonafluorobutanesulfonyl fluoride (1.05 mL, 6.00 mmol, 1.20 eq) in THF (1.00 mL) was added and stirring was continued at room temperature for 30 min. Water (5 mL) was added, the layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (solid load; pentane/EtOAc 40:1, 0.6 L) gave **186** (1.33 g, 71 %) as a colourless oil, **R_F** (pentane/EtOAc 40:1) 0.84; ¹H NMR (400 MHz, CDCl₃) δ: 7.50-7.43 (m, 2H, Ar), 7.43-7.37 (m, 1H, Ar), 7.34-7.28 (m, 2H, Ar); ¹³C NMR (100.6 MHz, CDCl₃) δ: 149.9 (Ar), 130.3 (Ar), 128.4 (Ar), 121.4 (Ar), 118.9-105.6 (m, 3 x CF₂, CF₃); ¹⁹F NMR (376.5 MHz, CDCl₃) δ: -80.84 (tt, 3F, *J* = 10.0, 2.0 Hz, CF₃), -109.03-109.15 (m, 2F, CF₂), -120.89-121.05 (m, 2F, CF₂), -125.87-126.04 (m, 2F, CF₂). Data were consistent with those in the literature.¹⁰⁴

General Procedure 13: Cross-Coupling of aryl bromides with (alkynyl)dimethyl aluminium

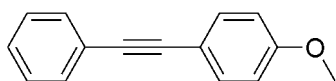
A flame-dried, stirrer-equipped Schlenk tube under argon was charged with AlMe_3 (1.00-4.00 mL of a 2.0 M solution in hexane, 2.00-8.00 mmol, 1.00 eq), $\text{MeN}(\text{SiMe}_3)_2$ (30.0-120 μL , 120-480 μmol , 6.00 mol%), and alkyne (2.40-9.60 mmol, 1.20 eq), and the reaction mixture was stirred at 25 $^\circ\text{C}$ for 16 h before adding toluene to give a 0.75 M solution. In a separate Schlenk or carousel tube, $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (15.5 mg, 15.0 μmol , 1.50 mol%) and DavePhos (11.8 mg, 30.0 μmol , 3.00 mol%) were dissolved in THF (3.00 mL). A portion of RCCAlMe_2 solution (2.00 mmol, 2.00 eq) was added, followed by aryl bromide (1.00 mmol, 1.00 eq) and THF (3.00 mL). The reaction mixture was heated at reflux for 5 h. Water (600 μL) was added followed by 1 M $\text{HCl}_{(\text{aq})}$ (3 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 3 mL). The solvent was removed under reduced pressure to give the crude product, which was purified by solid load flash column chromatography.

Diphenylacetylene 170



Using general procedure **13**, (phenylethynyl)dimethylaluminium (2.65 mL, 2.00 mmol), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (15.4 mg), DavePhos (12.0 mg), bromobenzene (105 μL , 1.00 mmol) and purification by flash column chromatography (pentane, 0.4 L) gave diphenylacetylene **170** (170 mg, 95 %) as long fine white needles, R_F (pentane) 0.46; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.61-7.53 (m, 4H, Ar), 7.42-7.32 (m, 6H, Ar); $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ : 131.6 (Ar), 128.3 (Ar), 128.2 (Ar), 123.3 (Ar), 89.4 (PhC). Data were consistent with those reported in the literature.¹⁶¹

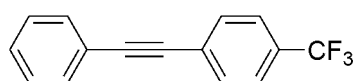
1-methoxy-4-(phenylethynyl)benzene 237



Using general procedure **13**, (phenylethynyl)dimethylaluminium (2.65 mL, 2.00 mmol), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (15.3 mg), DavePhos (11.8 mg), 4-bromoanisole

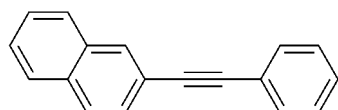
(125 μ L, 1.00 mmol) and purification by flash column chromatography (pentane/Et₂O 50:1, 0.4 L) gave 1-methoxy-4-(phenylethynyl)benzene **237** (183 mg, 88 %) as a light brown crystalline solid, *R*_F (pentane/Et₂O 50:1) 0.14; ¹H NMR (400 MHz, CDCl₃) δ : 7.56-7.45 (m, 4H, Ar), 7.39-7.29 (m, 3H, Ar), 6.93-6.85 (m, 2H, Ar), 3.84 (s, 3H, OCH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ : 159.6 (Ar), 133.0 (Ar), 131.4 (Ar), 128.3 (Ar), 127.9 (Ar), 123.6 (Ar), 115.4 (Ar), 114.0 (Ar), 89.3 (CC), 88.1 (CC), 55.3 (OCH₃). Data were consistent with those reported in the literature.¹⁶¹

1-(phenylethynyl)-4-(trifluoromethyl)benzene **238**



Using general procedure **13**, (phenylethynyl)dimethylaluminium (2.25 mL, 2.00 mmol), Pd₂(dba)₃·CHCl₃ (15.2 mg), DavePhos (11.9 mg), 4-bromobenzotrifluoride (140 μ L, 1.00 mmol) and purification by flash column chromatography (pentane, 0.7 L) gave 1-(phenylethynyl)-4-(trifluoromethyl)benzene **238** (239 mg, 97 %) as a fluffy white solid, *R*_F (pentane) 0.65; ¹H NMR (400 MHz, CDCl₃) δ : 7.67-7.59 (m, 4H, Ar), 7.59-7.52 (m, 2H, Ar), 7.41-7.35 (m, 3H, Ar); ¹³C NMR (100.6 MHz, CDCl₃) δ : 131.8 (Ar), 131.7 (Ar), 129.9 (d, ²J_{CF} = 33.0 Hz, CCF₃), 128.8 (Ar), 128.4 (Ar), 127.1 (d, J_{CF} = 1.5 Hz, CF₃CCHCHC), 125.3 (q, J_{CF} = 3.8 Hz, CHCCF₃), 123.9 (q, ¹J_{CF} = 272.0 Hz, CF₃), 122.6 (Ar), 91.7 (CC), 88.0 (CC). Data were consistent with those reported in the literature.¹⁶²

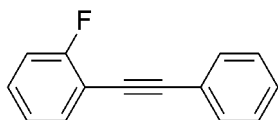
2-(phenylethynyl)naphthalene **239**



Using general procedure **13**, (phenylethynyl)dimethylaluminium (2.25 mL, 2.00 mmol), Pd₂(dba)₃·CHCl₃ (15.4 mg), DavePhos (11.8 mg), 2-bromonaphthalene (206 mg, 1.00 mmol) and purification by flash column chromatography (pentane, 0.55 L) gave 2-(phenylethynyl)naphthalene **239** (157 mg, 69 %) as an off-white solid, *R*_F (pentane) 0.26; ¹H NMR (400 MHz, CDCl₃) δ : 8.07 (s, 1H, Ar), 7.87-7.80 (m, 3H, Ar), 7.63-7.57 (m, 3H, Ar), 7.54-

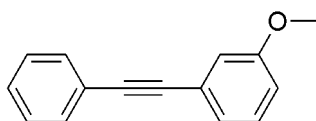
7.48 (m, 2H, Ar), 7.42-7.34 (m, 3H, Ar); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 133.0 (Ar), 132.8 (Ar), 131.7 (Ar), 131.4 (Ar), 128.4 (Ar), 128.4 (Ar), 128.3 (Ar), 128.0 (Ar), 127.8 (Ar), 126.6 (Ar), 126.5 (Ar), 123.3 (Ar), 120.6 (Ar), 89.8 (CC), 89.7 (CC). Data were consistent with those reported in the literature.¹⁶³

1-fluoro-2-(phenylethynyl)benzene **240**



Using general procedure **13**, (phenylethynyl)dimethylaluminium (2.15 mL, 2.00 mmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (15.3 mg), DavePhos (11.9 mg), 1-bromo-2-fluorobenzene (103 μL , 1.00 mmol) and purification by flash column chromatography (pentane, 0.55 L) gave 1-fluoro-2-(phenylethynyl)benzene **240** (128 mg, 65 %) as a colourless oil, R_F (pentane) 0.40; ^1H NMR (400 MHz, CDCl_3) δ : 7.63-7.50 (m, 3H, Ar), 7.42-7.28 (m, 4H, Ar), 7.18-7.09 (m, 2H, Ar); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 162.6 (d, $^1J_{\text{CF}} = 251.5$ Hz, CF), 133.4 (Ar), 131.7 (Ar), 129.9 (d, $J_{\text{CF}} = 7.7$ Hz, Ar), 128.6 (Ar), 128.3 (Ar), 123.9 (d, $J_{\text{CF}} = 3.8$ Hz, Ar), 122.9 (Ar), 115.5 (d, $^2J_{\text{CF}} = 19.9$ Hz, CHCF), 111.9 (d, $^2J_{\text{CF}} = 16.1$ Hz, PhCCC), 94.4 (d, $J_{\text{CF}} = 3.1$ Hz, PhCC), 82.7 (PhCC). Data were consistent with those reported in the literature.¹⁶⁴

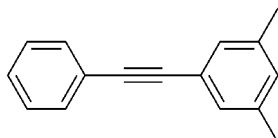
1-methoxy-3-(phenylethynyl)benzene **241**



Using general procedure **13**, (phenylethynyl)dimethylaluminium (2.15 mL, 2.00 mmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (15.4 mg), DavePhos (11.9 mg), 3-bromoanisole (126 μL , 1.00 mmol) and purification by flash column chromatography (pentane, 0.65 L; hexane, 0.7 L; hexane/ Et_2O 9:1, 0.1 L) gave 1-methoxy-3-(phenylethynyl)benzene **241** (179 mg, 86%) as a pale yellow solid, R_F (pentane) 0.11; ^1H NMR (400 MHz, CDCl_3) δ : 7.58-7.51 (m, 2H, Ar), 7.40-7.33 (m, 3H, Ar), 7.30-7.24 (m, 1H, MeOCCHCH), 7.15 (app dt, 1H, $J =$

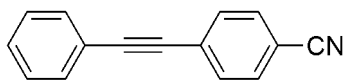
7.6, 1.2 Hz, Ar) 7.08 (dd, 1H, $J = 2.6, 1.4$ Hz, MeOCCHC), 6.91 (ddd, 1H, $J = 8.3, 2.6, 1.0$ Hz, Ar), 3.84 (s, 3H, OCH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ : 159.3 (Ar), 131.6 (Ar), 129.4 (Ar), 128.3 (Ar), 128.3 (Ar), 124.3 (Ar), 124.2 (Ar), 123.2 (Ar), 116.3 (Ar), 114.9 (Ar), 89.3 (CC), 89.2 (CC), 55.3 (OCH₃). Data were consistent with those reported in the literature.¹⁶⁵

1,3-dimethyl-5-(phenylethynyl)benzene **242**



Using general procedure **13**, (phenylethynyl)dimethylaluminium (2.20 mL, 2.00 mmol), Pd₂(dba)₃·CHCl₃ (15.8 mg), DavePhos (11.8 mg), 5-bromo-*m*-xylene (136 μ L, 1.00 mmol) and purification by flash column chromatography (pentane, 0.55 L) gave 1,3-dimethyl-5-(phenylethynyl)benzene **242** (196 mg, 95 %) as a colourless oil which crystallised on standing, R_F (pentane) 0.43; ¹H NMR (400 MHz, CDCl₃) δ : 7.60-7.52 (m, 2H, Ar), 7.42-7.32 (m, 3H, Ar), 7.22 (s, 2H, Ar), 7.01 (s, 1H, Ar), 2.35 (s, 6H, 2 x CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ : 137.9 (Ar), 131.6 (Ar), 130.2 (Ar), 129.3 (Ar), 128.3 (Ar), 128.1 (Ar), 123.4 (Ar), 122.8 (Ar), 89.7 (CC), 88.7 (CC), 21.1 (CH₃). Data were consistent with those reported in the literature.¹⁶³

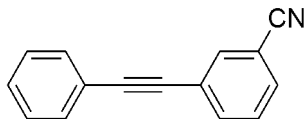
4-(phenylethynyl)benzonitrile **243**



Using general procedure **13**, (phenylethynyl)dimethylaluminium (2.25 mL, 2.00 mmol), Pd₂(dba)₃·CHCl₃ (15.7 mg), DavePhos (11.8 mg), 4-bromobenzonitrile (183 mg, 1.01 mmol) and purification by flash column chromatography (pentane/Et₂O 9:1, 0.6 L) gave 4-(phenylethynyl)benzonitrile **243** (173 mg, 84 %) as a pale yellow-orange solid, R_F (pentane/Et₂O 9:1) 0.60; ¹H NMR (400 MHz, CDCl₃) δ : 7.67-7.59 (m, 4H, Ar), 7.58-7.53 (m, 2H, Ar), 7.42-7.37 (m, 3H, Ar); ¹³C NMR (100.6 MHz, CDCl₃) δ : 132.0 (Ar), 132.0 (Ar), 131.8 (Ar), 129.1 (Ar), 128.5 (Ar), 128.2 (Ar), 122.2 (Ar), 118.5 (CN),

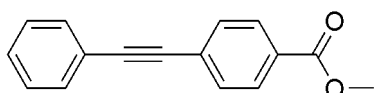
111.4 (Ar), 93.8 (CC), 87.7 (CC). Data were consistent with those reported in the literature.¹⁶⁵

3-(phenylethynyl)benzonitrile **244**



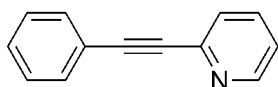
Using general procedure **13**, (phenylethynyl)dimethylaluminium (2.25 mL, 2.00 mmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (15.8 mg), DavePhos (12.0 mg), 3-bromobenzonitrile (182 mg, 1.00 mmol) and purification by flash column chromatography (pentane/ Et_2O 9:1, 0.6 L) gave 3-(phenylethynyl)benzonitrile **244** (199 mg, 98 %) as a red-orange solid, R_F (pentane/ Et_2O 9:1) 0.47; ^1H NMR (400 MHz, CDCl_3) δ : 7.83-7.80 (m, 1H, Ar), 7.75 (dt, 1H, $J = 7.9$, 1.4 Hz, Ar), 7.61 (dt, 1H, $J = 7.8$, 1.4 Hz, Ar), 7.58-7.53 (m, 2H, Ar), 7.48 (td, 1H, $J = 7.9$, 0.4 Hz, Ar), 7.41-7.35 (m, 3H, Ar); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 135.6 (Ar), 134.9 (Ar), 131.7 (Ar), 131.3 (Ar), 129.2 (Ar), 129.0 (Ar), 128.5 (Ar), 124.9 (Ar), 122.2 (Ar), 118.1 (CN), 112.9 (Ar), 91.8 (CC), 86.9 (CC). Data were consistent with those reported in the literature.¹⁶¹

Methyl 4-(phenylethynyl)benzoate **245**



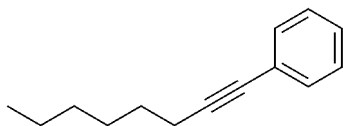
Using general procedure **13**, (phenylethynyl)dimethylaluminium (2.65 mL, 2.00 mmol), $\text{Pd}(\text{dba})_2$ (17.2 mg, 29.9 μmol , 2.99 mol%), DavePhos (11.8 mg), methyl 4-bromobenzoate (215 mg, 1.00 mmol) and purification by flash column chromatography (pentane/ Et_2O 9:1, 0.4 L) gave methyl 4-(phenylethynyl)benzoate **245** (228 mg, 96 %) as an amber crystalline solid, R_F (pentane/ Et_2O 9:1) 0.53; ^1H NMR (400 MHz, CDCl_3) δ : 8.06-8.01 (m, 2H, Ar), 7.63-7.52 (m, 4H, Ar), 7.40-7.35 (m, 3H, Ar), 3.94 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 166.5 (CO), 131.7 (Ar), 131.5 (Ar), 129.5 (Ar), 129.5 (Ar), 128.7 (Ar), 128.4 (Ar), 128.0 (Ar), 122.7 (Ar), 92.3 (CC), 88.6 (CC), 52.2 (CH_3). Data were consistent with those reported in the literature.¹⁶⁶

2-(phenylethynyl)pyridine **246**



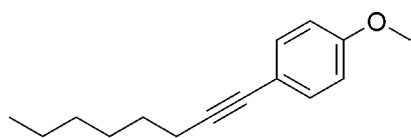
Using general procedure **13**, (phenylethynyl)dimethylaluminium (2.25 mL, 2.00 mmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (15.5 mg), DavePhos (11.9 mg), 2-bromopyridine (98.0 μL , 1.00 mmol) and purification by flash column chromatography (pentane/ Et_2O 4:1, 0.7 L) gave 2-(phenylethynyl)pyridine **246** (147 mg, 52 %, inseparable from impurities) as an amber oil, ^1H NMR (400 MHz, CDCl_3) δ : 8.62 (ddd, 1H, $J = 4.8, 1.6, 0.9$ Hz, NCH), 7.67 (td, 1H, $J = 7.8, 1.8$ Hz, NCHCHCH), 7.63-7.58 (m, 2H, Ph), 7.52 (dt, 1H, $J = 7.8, 1.0$ Hz, NCHCHCHCH), 7.39-7.33 (m, 3H, Ph), 7.23 (ddd, 1H, $J = 7.6, 4.8, 1.2$ Hz, NCHCH); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 150.0 (NCH), 143.4 (NC), 136.1 (NCHCHCH), 132.0 (Ph), 128.9 (Ph), 128.3 (Ph), 127.1 (NCHCHCHCH), 122.7 (NCHCH), 122.2 (Ph), 89.2 (CC), 88.6 (CC). Data were consistent with those reported in the literature.¹⁶⁷

Oct-1-ynylbenzene **247**



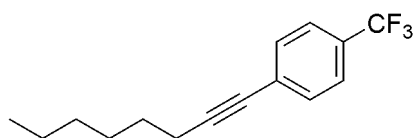
Using General Procedure **13**, AlMe_3 (2.00 mL of a 2.0 M solution in hexane, 4.00 mmol), $\text{MeN}(\text{SiMe}_3)_2$ (60.0 μL , 240 μmol), and 1-octyne (710 μL , 4.80 mmol), taking a portion of $\text{C}_6\text{H}_{13}\text{CCAlMe}_2$ solution (2.65 mL, 2.00 mmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (15.4 mg, 14.9 μmol , 1.49 mol%), DavePhos (11.8 mg, 30.0 μmol , 3.00 mol%), bromobenzene (105 μL , 1.00 mmol) and purification by flash column chromatography (pentane, 0.4 L) gave oct-1-ynylbenzene **247** (155 mg, 83 %) as a yellow oil, R_F (pentane) 0.55; ^1H NMR (400 MHz, CDCl_3) δ : 7.43-7.37 (m, 2H, Ar), 7.31-7.25 (m, 3H, Ar), 2.41 (t, 2H, $J = 7.1$ Hz, CCCH_2), 1.66-1.56 (m, 2H, CH_2), 1.51-1.42 (m, 2H, CH_2), 1.40-1.25 (m, 4H, 2 x CH_2), 0.91 (t, 3H, $J = 7.0$ Hz, CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 131.5 (Ar), 128.2 (Ar), 127.4 (Ar), 124.1 (Ar), 90.5 (CC), 80.5 (CC), 31.4 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 22.6 (CH_2), 19.4 (CH_2), 14.1 (CH_3). Data were consistent with those reported in the literature.¹⁶⁸

1-(4-Methoxyphenyl)-1-octyne **248**



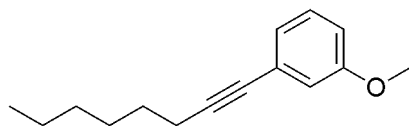
Using General Procedure **13**, $\text{C}_6\text{H}_{13}\text{CCAlMe}_2$ solution (2.60 mL, 2.00 mmol), $\text{Pd}(\text{dba})_2$ (17.4 mg, 30.3 μmol , 3.03 mol%), DavePhos (11.7 mg, 29.7 μmol , 2.97 mol%), 4-bromoanisole (125 μL , 1.00 mmol) and purification by flash column chromatography (pentane, 0.6 L; pentane/ Et_2O 9:1, 0.5 L) gave **248** (203 mg, 94 %) as a pale brown oil, R_F (pentane) 0.18; ^1H NMR (400 MHz, CDCl_3) δ : 7.36-7.31 (m, 2H, Ar), 6.85-6.79 (m, 2H, Ar), 3.81 (s, 3H, OCH_3), 2.39 (t, 2H, $J = 7.1$ Hz, CCCH_2), 1.65-1.55 (m, 2H, CH_2), 1.50-1.41 (m, 2H, CH_2), 1.40-1.26 (m, 4H, 2 x CH_2), 0.91 (t, 3H, $J = 6.9$ Hz, CH_2CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 159.0 (Ar), 132.8 (Ar), 116.3 (Ar), 113.8 (Ar), 88.8 (CC), 80.2 (CC), 55.2 (OCH_3), 31.4 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 22.6 (CH_2), 19.4 (CH_2), 14.1 (CH_2CH_3). Data were consistent with those reported in the literature.¹⁶⁹

1-(Oct-1-ynyl)-4-(trifluoromethyl)benzene **249**



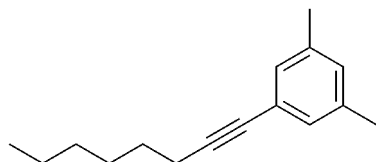
Using General Procedure **13**, $\text{C}_6\text{H}_{13}\text{CCAlMe}_2$ solution (2.60 mL, 2.00 mmol), $\text{Pd}(\text{dba})_2$ (17.3 mg, 30.0 μmol , 3.00 mol%), DavePhos (11.6 mg, 29.5 μmol , 2.95 mol%), 4-bromobenzotrifluoride (140 μL , 1.00 mmol) and purification by flash column chromatography (pentane, 0.6 L) gave **249** (232 mg, 92 %) as a pale yellow oil, R_F (pentane) 0.67; ^1H NMR (400 MHz, CDCl_3) δ : 7.54 (d, 2H, $J = 8.2$ Hz, Ar), 7.49 (d, 2H, $J = 8.2$ Hz, Ar), 2.43 (t, 2H, $J = 7.1$ Hz, CCCH_2), 1.67-1.58 (m, 2H, CH_2), 1.51-1.41 (m, 2H, CH_2), 1.40-1.28 (m, 4H, 2 x CH_2), 0.91 (t, 3H, $J = 6.9$ Hz, CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 131.7 (Ar), 128.0 (Ar), 125.1 (q, $J_{\text{CF}} = 3.8$ Hz, Ar), 124.0 (q, $^1J_{\text{CF}} = 273.0$ Hz, CF_3), 93.4 (CC), 79.5 (CC), 31.3 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 22.5 (CH_2), 19.4 (CH_2), 14.0 (CH_3), *ipso*-Ar not observed. Data were consistent with those reported in the literature.¹⁷⁰

1-(3-Methoxyphenyl)-1-octyne **250**



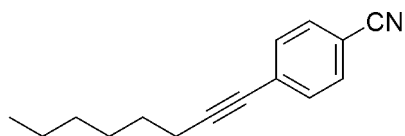
Using General Procedure **13**, $\text{C}_6\text{H}_5\text{CCAlMe}_2$ solution (2.35 mL, 2.00 mmol), $\text{Pd}(\text{dba})_2$ (17.1 mg, 29.7 μmol , 2.97 mol%), DavePhos (11.7 mg, 29.7 μmol , 2.97 mol%), 3-bromoanisole (126 μL , 1.00 mmol) and purification by flash column chromatography (pentane, 1.4 L; pentane/ Et_2O 9:1, 0.2 L) gave **250** (189 mg, 87 %) as a pale yellow oil, R_F (pentane) 0.18; ^1H NMR (400 MHz, CDCl_3) δ : 7.20 (t, 1H, $J = 8.2$ Hz, Ar), 7.04-7.00 (m, 1H, Ar), 6.97-6.94 (m, 1H, Ar), 6.86-6.82 (m, 1H, Ar), 3.80 (s, 3H, OCH_3), 2.42 (t, 2H, $J = 7.1$ Hz, CCCH_2), 1.68-1.57 (m, 2H, CH_2), 1.53-1.43 (m, 2H, CH_2), 1.42-1.27 (m, 4H, 2 x CH_2), 0.96-0.90 (m, 3H, CH_2CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 159.2 (Ar), 129.2 (Ar), 125.1 (Ar), 124.1 (Ar), 116.4 (Ar), 114.0 (Ar), 90.3 (CC), 80.4 (CC), 55.1 (OCH_3), 31.3 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 22.5 (CH_2), 19.4 (CH_2), 14.0 (CH_2CH_3). Data were consistent with those reported in the literature.¹⁷¹

1,3-dimethyl-5-(oct-1-ynyl)benzene **251**



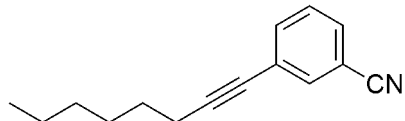
Using General Procedure **13**, $\text{C}_6\text{H}_5\text{CCAlMe}_2$ solution (2.35 mL, 2.00 mmol), $\text{Pd}(\text{dba})_2$ (17.1 mg, 29.7 μmol , 2.97 mol%), DavePhos (11.8 mg, 30.0 μmol , 3.00 mol%), 5-bromo-*m*-xylene (136 μL , 1.00 mmol) and purification by flash column chromatography (pentane, 0.4 L) gave **251** (174 mg, 81 %) as a yellow oil, R_F (pentane) 0.60; IR (CHCl_3) 3426, 2930, 2858, 1599, 1466, 1378 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.09 (s, 2H, Ar), 6.94 (s, 1H, Ar), 2.47-2.41 (m, 2H, CH_2), 2.32 (s, 6H, 2 x ArCH_3), 1.71-1.60 (m, 2H, CH_2), 1.56-1.47 (m, 2H, CH_2), 1.45-1.30 (m, 4H, 2 x CH_2), 1.01-0.92 (m, 3H, CH_2CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 137.6 (Ar), 129.3 (Ar), 129.2 (Ar), 123.7 (Ar), 89.6 (CC), 80.7 (CC), 31.4 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 22.6 (CH_2), 21.0 (ArCH_3), 19.4 (CH_2), 14.0 (CH_2CH_3); HRMS (EI), m/z for $\text{C}_{16}\text{H}_{22}$ (M^+), calcd. 214.1722, found 214.1721.

4-(Oct-1-ynyl)benzonitrile **252**



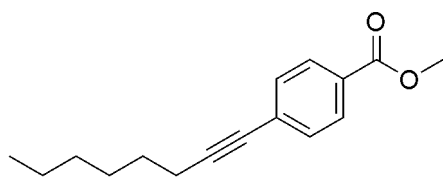
Using General Procedure **13**, $\text{C}_6\text{H}_{13}\text{CCAlMe}_2$ solution (2.30 mL, 2.00 mmol), $\text{Pd}(\text{dba})_2$ (17.3 mg, 30.0 μmol , 3.03 mol%), DavePhos (12.0 mg, 30.5 μmol , 3.08 mol%), 4-bromobenzonitrile (180 mg, 989 μmol) and purification by flash column chromatography (pentane/ Et_2O 19:1, 0.6 L) gave **252** (173 mg, 82 %) as an amber oil, R_F (pentane/ Et_2O 19:1) 0.47; ^1H NMR (400 MHz, CDCl_3) δ : 7.58-7.54 (m, 2H, Ar), 7.47-7.43 (m, 2H, Ar), 2.42 (t, 2H, $J = 7.1$ Hz, CCCH_2), 1.65-1.56 (m, 2H, CH_2), 1.49-1.40 (m, 2H, CH_2), 1.39-1.26 (m, 4H, 2 x CH_2), 0.90 (t, 3H, $J = 6.9$ Hz, CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 132.0 (Ar), 131.8 (Ar), 129.1 (Ar), 118.6 (CN), 110.7 (Ar), 95.7 (CC), 79.4 (CC), 31.2 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 22.5 (CH_2), 19.4 (CH_2), 14.0 (CH_3). Data were consistent with those reported in the literature.¹⁷²

3-(Oct-ynyl)benzonitrile **253**



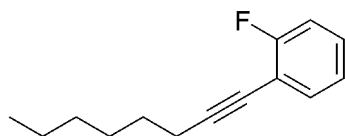
Using General Procedure **13**, $\text{C}_6\text{H}_{13}\text{CCAlMe}_2$ solution (2.30 mL, 2.00 mmol), $\text{Pd}(\text{dba})_2$ (17.4 mg, 30.3 μmol , 3.03 mol%), DavePhos (12.1 mg, 30.7 μmol , 3.04 mol%), 3-bromobenzonitrile (183 mg, 1.01 mmol) and purification by flash column chromatography (pentane/ Et_2O 19:1, 0.4 L) gave **253** (183 mg, 86 %) as a yellow oil, R_F (pentane/ Et_2O 19:1) 0.44; IR (CHCl_3) 3394, 2931, 2859, 2233, 1598, 1572, 1478 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.66 (t, 1H, $J = 1.6$ Hz, Ar), 7.59 (dt, 1H, $J = 7.8, 1.4$ Hz, Ar), 7.53 (dt, 1H, $J = 7.8, 1.4$ Hz, Ar), 7.39 (t, 1H, $J = 7.7$ Hz, Ar), 2.41 (t, 2H, $J = 7.1$ Hz, CCCH_2), 1.65-1.56 (m, 2H, CH_2), 1.50-1.40 (m, 2H, CH_2), 1.40-1.27 (m, 4H, 2 x CH_2), 0.91 (t, 3H, $J = 6.9$ Hz, CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 135.6 (Ar), 134.9 (Ar), 130.6 (Ar), 129.0 (Ar), 125.7 (Ar), 118.2 (CN), 112.6 (Ar), 93.4 (CC), 78.5 (CC), 31.3 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 22.5 (CH_2), 19.3 (CH_2), 14.0 (CH_3); HRMS (ESI, pos.), m/z for $\text{C}_{15}\text{H}_{17}\text{N}$ ($[\text{M} + \text{Na}]^+$), calcd. 234.1259, found 234.1246. Reported in the literature without spectroscopic data.¹⁷³

Methyl 4-(oct-1-ynyl)benzoate **254**



Using General Procedure **13**, $\text{C}_6\text{H}_{13}\text{CCAlMe}_2$ solution (2.30 mL, 2.00 mmol), $\text{Pd}(\text{dba})_2$ (17.0 mg, 29.6 μmol , 2.96 mol%), DavePhos (12.1 mg, 30.7 μmol , 3.07 mol%), methyl 4-bromobenzoate (215 mg, 1.00 mmol) and purification by flash column chromatography (pentane/ Et_2O 9:1, 0.4 L) gave **254** (141 mg, 58 %) as a yellow oil, R_F (pentane/ Et_2O 9:1) 0.64; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.98-7.93 (m, 2H, Ar), 7.47-7.42 (m, 2H, Ar), 3.91 (s, 3H, CO_2CH_3), 2.43 (t, 2H, $J = 7.1$ Hz, CCCH_2), 1.66-1.57 (m, 2H, CH_2), 1.51-1.41 (m, 2H, CH_2), 1.40-1.27 (m, 4H, 2 x CH_2), 0.91 (t, 3H, $J = 7.2$ Hz, CH_2CH_3); $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ : 166.6 (C=O), 131.4 (Ar), 129.4 (Ar), 128.9 (Ar), 128.8 (Ar), 94.0 (CC), 80.1 (CC), 52.1 (CO_2CH_3), 31.3 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 22.5 (CH_2), 19.5 (CH_2), 14.0 (CH_3). Data were consistent with those reported in the literature.¹⁷⁰

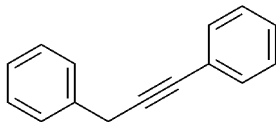
1-fluoro-2-(oct-1-ynyl)benzene **255**



Using General Procedure **13**, $\text{C}_6\text{H}_{13}\text{CCAlMe}_2$ solution (2.30 mL, 2.00 mmol), $\text{Pd}(\text{dba})_2$ (17.1 mg, 29.7 μmol , 2.97 mol%), DavePhos (11.7 mg, 29.7 μmol , 2.97 mol%), 1-bromo-2-fluorobenzene (103 μL , 1.00 mmol) and purification by flash column chromatography (pentane, 0.4 L) gave **255** (138 mg, 67 %) as a yellow oil, R_F (pentane) 0.59; IR (CHCl_3) 3426, 2931, 2859, 2234, 1574, 1493, 1454, 1379, 1330, 1256, 1217, 1104, 1032 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.44 (td, 1H, $J = 7.4, 1.8$ Hz, Ar), 7.32-7.24 (m, 1H, Ar), 7.13-7.06 (m, 2H, Ar), 2.50 (t, 2H, $J = 7.1$ Hz, CCCH_2), 1.73-1.63 (m, 2H, CH_2), 1.58-1.48 (m, 2H, CH_2), 1.45-1.31 (m, 4H, 2 x CH_2), 0.96 (t, 3H, $J = 7.0$ Hz, CH_3); $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ : 162.8 (d, $^1J_{\text{CF}} = 250.0$ Hz, CF), 133.5 (d, $J_{\text{CF}} = 1.5$ Hz, Ar), 129.0 (d, $J_{\text{CF}} = 7.5$ Hz, Ar), 123.7 (d, $J_{\text{CF}} = 4.0$ Hz, Ar), 115.3 (d, $J_{\text{CF}} = 21.5$ Hz, Ar), 112.6 (d, $J_{\text{CF}} = 16.0$ Hz, Ar), 96.0 (d, $J_{\text{CF}} = 4.0$ Hz, CC),

73.9 (CC), 31.3 (CH₂), 28.6 (CH₂), 28.5 (CH₂), 22.5 (CH₂), 19.6 (CH₂), 14.0 (CH₃); **HRMS** (ESI, pos.), *m/z* for C₁₄H₁₇F ([M + Na]⁺), calcd. 227.1212, found 226.9519. Reported in the literature without spectroscopic data.¹⁷⁴

Prop-1-yne-1,3-diyl dibenzene **256**



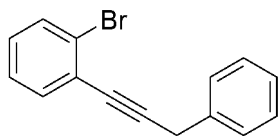
Using General Procedure **13**, AlMe₃ (1.00 mL of a 2.0 M solution in hexane, 2.00 mmol, 2.00 eq), MeN(SiMe₃)₂ (30.0 μL, 120 μmol, 12.0 mol%), and 3-phenyl-1-propyne (300 μL, 2.40 mmol, 2.40 eq), toluene (1.35 mL), Pd(dba)₂ (17.3 mg, 30.0 μmol, 3.00 mol%), DavePhos (11.9 mg, 30.2 μmol, 3.02 mol%), PhCH₂CCAlMe₂ solution (2.65 mL, 2.00 mmol, 2.00 eq), bromobenzene (105 μL, 1.00 mmol, 1.00 eq) and purification by flash column chromatography (pentane, 0.6 L) gave prop-1-yne-1,3-diyl dibenzene **256** (175 mg, 91 %) as a pale yellow oil, *R_F* (pentane) 0.33; ¹H NMR (400 MHz, CDCl₃) δ: 7.52-7.25 (m, 10H, Ar), 3.87 (s, 2H, CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ: 136.7 (Ar), 131.6 (Ar), 128.5 (Ar), 128.2 (Ar), 127.9 (Ar), 127.8 (Ar), 126.6 (Ar), 123.7 (Ar), 87.5 (CC), 82.6 (CC), 25.7 (PhCH₂). Data were consistent with those reported in the literature.¹⁶³

Prop-1-yne-1,3-diyl dibenzene **256**

Using General Procedure **13**, Pd(dba)₂ (34.8 mg, 60.5 μmol, 3.03 mol%), DavePhos (23.7 mg, 60.2 μmol, 3.01 mol%), PhCH₂CCAlMe₂ solution (5.35 mL, 4.00 mmol), bromobenzene (211 μL, 2.00 mmol) and purification by flash column chromatography (pentane, 0.6 L) gave prop-1-yne-1,3-diyl dibenzene **256** (351 mg, 91 %) as a pale yellow oil. Data as above.

5.4.2 Towards the Synthesis of Tetracenes

1-bromo-2-(3-phenylprop-1-ynyl)benzene **188**



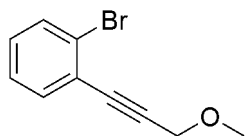
Under argon, 3-phenyl-1-propyne (124 μL , 1.00 mmol, 1.00 eq) was added to a mixture of 1-bromo-2-iodobenzene (128 μL , 1.00 mmol, 1.00 eq), $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2$ (35.0 mg, 49.9 μmol , 4.99 mol%) and CuI (19.2 mg, 101 μmol , 10.1 mol%) in Et_3N (10.0 mL). The reaction mixture was stirred at room temperature for 21 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL) was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (solid load; pentane 0.6 L) gave **188** (202 mg, 75 %) as a colourless oil, R_{F} (pentane) 0.55; **IR** (CHCl_3) 3456, 3063, 3029, 2234, 1602, 1494, 1469, 1453, 1433, 1052, 1027 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ : 7.60 (dd, 1H, $J = 8.0, 1.3$ Hz, Ar), 7.52-7.46 (m, 3H, Ar), 7.37 (t, 2H, $J = 7.3$ Hz, Ar), 7.31-7.23 (m, 2H, Ar), 7.16 (td, 1H, $J = 7.3, 1.5$ Hz, Ar), 3.93 (s, 2H, CH_2); **^{13}C NMR** (100.6 MHz, CDCl_3) δ : 136.3 (Ar), 133.4 (Ar), 132.3 (Ar), 129.0 (Ar), 128.5 (Ar), 128.0 (Ar), 126.9 (Ar), 126.7 (Ar), 125.7 (Ar), 125.5 (Ar), 92.4 (CC), 81.4 (CC), 25.9 (CH_2); **HRMS** (EI), m/z for $\text{C}_{15}\text{H}_{11}^{79}\text{Br}$ (M^+), calcd. 270.0044, found 270.0043

1-bromo-2-(3-phenylprop-1-ynyl)benzene **188**

Under argon, 3-phenyl-1-propyne (310 μL , 2.49 mmol, 1.00 eq) was added to a mixture of 1-bromo-2-iodobenzene (320 μL , 2.49 mmol, 1.00 eq), $\text{PdCl}_2(\text{PPh}_3)_2$ (174 mg, 248 μmol , 9.96 mol%) and CuI (94.7 mg, 497 μmol , 20.0 mol%) in Et_3N (50.0 mL). The reaction mixture was stirred at room temperature for 21 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (50 mL) was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column

chromatography (solid load; pentane 1.6 L), followed by drying under high vacuum gave **188** (453 mg, 67 %) as a colourless oil. Data as above.

1-bromo-2-(3-methoxyprop-1-ynyl)benzene **189**



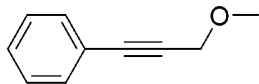
Under argon, methyl propargyl ether (84.0 μ L, 1.00 mmol, 1.00 eq) was added to a mixture of 1-bromo-2-iodobenzene (128 μ L, 1.00 mmol, 1.00 eq), $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2$ (35.5 mg, 50.6 μ mol, 5.06 mol%) and CuI (19.2 mg, 101 μ mol, 10.1 mol%) in Et_3N (10.0 mL). The reaction mixture was stirred at room temperature for 21 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL) was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (solid load; pentane/ Et_2O 9:1, 0.7 L) gave **189** (145 mg, 64 %) as a colourless oil, R_F (pentane/ Et_2O 9:1) 0.95; **IR** (CHCl_3) 3417, 2990, 2932, 2822, 1587, 1558, 1469, 1434, 1354, 1187, 1099 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ : 7.59 (dd, 1H, J = 8.0, 1.0 Hz, Ar), 7.49 (dd, 1H, J = 7.7, 1.7 Hz, Ar), 7.27 (td, 1H, J = 7.5, 1.3 Hz, Ar), 7.18 (td, 1H, J = 7.9, 1.8 Hz, Ar), 4.39 (s, 2H, CH_2), 3.51 (s, 3H, CH_3); **^{13}C NMR** (100.6 MHz, CDCl_3) δ : 133.5 (Ar), 132.4 (Ar), 129.6 (Ar), 127.0 (Ar), 125.5 (Ar), 124.8 (Ar), 89.7 (CC), 84.9 (CC), 60.3 (CH_2), 57.7 (CH_3); **HRMS** (EI), m/z for $\text{C}_{10}\text{H}_9^{79}\text{BrO}$ (M^+), calcd. 223.9837, found 223.9841.

1-bromo-2-(3-methoxyprop-1-ynyl)benzene **189**

Under argon, methyl propargyl ether (420 μ L, 5.00 mmol, 1.00 eq) was added to a mixture of 1-bromo-2-iodobenzene (640 μ L, 5.00 mmol, 1.00 eq), $\text{PdCl}_2(\text{PPh}_3)_2$ (174 mg, 248 μ mol, 4.96 mol%) and CuI (96.2 mg, 505 μ mol, 10.1 mol%) in Et_3N (50.0 mL). The reaction mixture was stirred at room temperature for 21 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (50 mL) was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column

chromatography (solid load; pentane 0.6 L; pentane/Et₂O 30:1, 0.5 L) gave **189** (729 mg, 65 %) as a colourless oil. Data as above.

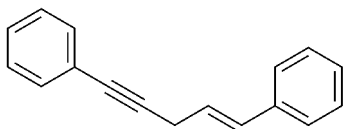
(3-methoxyprop-1-ynyl)benzene **191**



Under argon, methyl propargyl ether (169 μ L, 2.00 mmol, 1.00 eq) was added to a mixture of iodobenzene (224 μ L, 2.00 mmol, 1.00 eq), Pd(Ph₃P)₂Cl₂ (70.4 mg, 100 μ mol, 5.02 mol%) and CuI (38.3 mg, 201 μ mol, 10.1 mol%) in Et₃N (20.0 mL), and the reaction mixture was stirred at room temperature for 21 h. Saturated NH₄Cl_(aq) (20 mL) was added and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (solid load; pentane, 0.65 L; pentane/Et₂O 9:1, 0.2 L) gave **191** (222 mg, 76 %) as a pale yellow oil, *R*_F (pentane/Et₂O 9:1) 0.64; ¹H NMR (400 MHz, CDCl₃) δ : 7.50-7.43 (m, 2H, Ar), 7.35-7.30 (m, 3H, Ar), 4.34 (s, 2H, CH₂), 3.47 (s, 3H, CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ : 131.7 (Ar), 128.4 (Ar), 128.3 (Ar), 122.6 (Ar), 86.3 (CC), 84.9 (CC), 60.4 (CH₂), 57.7 (CH₃). Data were consistent with those in the literature.¹⁶¹

5.4.3 Cinnamyl Bromide Coupling

(*E*)-Pent-1-en-4-yne-1,5-diyl dibenzene **176**



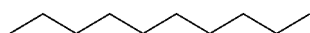
A flame-dried, stirrer-equipped 2 neck round-bottomed flask fitted with reflux condenser under argon was charged with EtMgBr (2.65 mL of a 3.4 M solution in Et₂O, 9.00 mmol). At 50 °C, a solution of phenylacetylene (990 μ L, 9.00 mmol) in Et₂O (7.20 mL) was added dropwise and the mixture was stirred at this temperature for 45 min then allowed to cool to room temperature. In a separate Schlenk tube, cinnamyl bromide (1.00 mL of a 0.31 M solution in THF, 310 μ mol, 1.00 eq) was added to

1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride **193** (5.3 mg, 16 μmol , 5.0 mol%). A portion of Grignard solution (1.80 mL, 0.83 M, 1.50 mmol, 4.84 eq) was added and the reaction mixture was heated at 40 °C for 24 h. 1 M $\text{HCl}_{(\text{aq})}$ (2 mL) and Et_2O (3 mL) were added, the layers were separated and the aqueous phase was extracted with Et_2O (2 x 3 mL). The combined organic extracts were evaporated under reduced pressure to give the crude product. Proton NMR spectroscopy showed this to be a 98:2 mixture of enyne **176** and cinnamyl bromide.

5.5 Hydroalumination of Alkenes and Alkynes

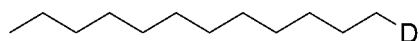
5.5.1 Hydroalumination of Alkenes

Decane **203**



A flame-dried, stirrer-equipped Schlenk flask under argon was charged with LiAlH_4 (113 mg, 2.97 mmol, 1.00 eq) and AlBr_3 (13.0 mL of a 0.66 M solution in hexane, 8.58 mmol, 2.89 eq) was added. The mixture was stirred at room temperature for 1 h. A solution of 1-decene (2.20 mL, 11.50 mmol, 3.87 eq) in hexane (7.50 mL) was added dropwise and the reaction mixture was heated at 40 °C for 15 min. Water (5 mL) was added dropwise, the layers were separated and the organic phase was evaporated under reduced pressure to give the crude product. Proton NMR spectroscopy showed full conversion to decane, no $\text{C}=\text{C}$ bond remained.

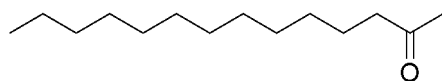
(1- ^2H)dodecane **204**



A flame-dried, stirrer-equipped Schlenk tube under argon was charged with a 6 M slurry of LiAlH_4 in Et_2O (500 μL , 3.00 mmol, 1.00 eq). Benzene (2.50 mL) was added, and the majority of solvent was removed under high vacuum. Under Ar, AlBr_3 (3.50 mL of a 2.59 M solution in benzene, 9.07 mmol, 3.02 eq) was added and the reaction mixture was stirred at room temperature for 1 h. A solution of 1-dodecene (2.55 mL, 11.5 mmol, 3.83 eq) in benzene

(7.50 mL) was added dropwise and the reaction mixture was heated at 40 °C for 30 min. D₂O (1.00 mL) was added dropwise and the mixture was stirred for 10 min. At room temperature, water (4 mL) was added, the layers were separated and the aqueous phase was extracted with Et₂O (2 x 5 mL). The combined organic extracts were evaporated under reduced pressure to give the crude product. The crude product was analysed by GC-MS, which indicated 62 % deuterium incorporation.

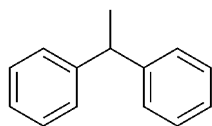
Tetradecan-2-one **206**



A flame-dried, stirrer-equipped Schlenk tube under argon was charged with a 6 M slurry of LiAlH₄ in Et₂O (500 µL, 3.00 mmol, 1.00 eq). Benzene (2.50 mL) was added before the mixture was evaporated to dryness under high vacuum. Under argon, a solution of AlBr₃ in benzene (3.50 mL of a 2.55 M solution, 8.93 mmol, 2.98 eq) was added and the reaction mixture was stirred at room temperature for 1 h. A solution of 1-dodecene (2.55 mL, 11.5 mmol, 3.83 eq) in benzene (7.50 mL) was added dropwise and the reaction mixture was heated at 40 °C for 30 min. The solvent was removed under high vacuum and the residue was redissolved in CH₂Cl₂ (12.5 mL). A solution of acetyl chloride (0.90 mL, 13.0 mmol, 4.33 eq) in CH₂Cl₂ (2.50 mL) was added dropwise at –20 °C and the reaction mixture was stirred at this temperature for 1 h, then at 25 °C for 30 min. H₂O (5 mL) was added, the layers were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 5 mL). The organic extracts were filtered and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (solid load; pentane/Et₂O 9:1; 0.8 L) gave **206** (1.15 g, 47 %) as a light amber oil, *R*_F (pentane/Et₂O 9:1) 0.46; ¹H NMR (400 MHz, CDCl₃) δ: 2.39 (t, 2H, *J* = 7.5 Hz, CH₂CO), 2.11 (s, 3H, CH₃CO), 1.59-1.49 (m, 2H, CH₂), 1.32-1.17 (m, 18H, 9 x CH₂), 0.86 (t, 3H, *J* = 6.6 Hz, CH₂CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ: 209.2 (CO), 43.7 (CH₂CO), 31.9 (CH₂), 29.7 (CH₂), 29.6 (CH₂), 29.6 (CH₃CO), 29.5 (CH₂), 29.4 (CH₂), 29.4 (CH₂), 29.3 (CH₂), 29.1 (CH₂), 23.8 (CH₂), 22.6 (CH₂), 14.0 (CH₂CH₃). Data were consistent with those reported in the literature.¹⁷⁵

5.5.2 Hydroalumination of Alkynes

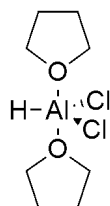
1,1-Diphenylethane **209**



A flame-dried, stirrer-equipped Schlenk tube under argon was charged with LiAlH_4 (37.9 mg, 1.00 mmol, 1.00 eq) and a solution of AlBr_3 in benzene (3.40 mL of a 0.90 M solution, 3.06 mmol, 3.06 eq) was added. A solution of 1-phenyl-2-trimethylsilylacetylene (390 μL , 2.00 mmol, 2.00 eq) in benzene (10.0 mL) was added dropwise and the reaction mixture was stirred at room temperature for 15 min. Water (2 mL) was added, the layers were separated and the aqueous phase was extracted with Et_2O (2 x 3 mL). The solvent was evaporated under reduced pressure to give the crude product. Proton and ^{13}C NMR spectroscopy showed the presence of 57 % of 1,1-diphenylethane **209**; ^1H NMR (400 MHz, CDCl_3) δ : 7.45-7.23 (m, 10H, Ar), 4.25 (q, 1H, $J = 7.2$ Hz, CHCH_3), 1.74 (d, 3H, $J = 7.2$ Hz, CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 146.3 (Ar), 128.3 (Ar), 127.6 (Ar), 126.0 (Ar), 44.7 (CH), 21.8 (CH_3). Data were consistent with those reported in the literature.¹⁷⁶

5.5.3 Hydroalumination-Cross-Coupling of Alkynes with Aryl Halides

Dichloroalane(bis-tetrahydrofuran) adduct **211**



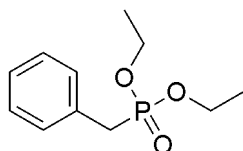
Aluminium trichloride (11.0 g, 82.5 mmol, 2.94 eq) was pulverised with a glass stick in a Schlenk tube under argon. At $-78\text{ }^\circ\text{C}$, Et_2O (40.0 mL) was added slowly. The cold bath was removed and the suspension stirred until all solids dissolved. The solution was added to a suspension of LiAlH_4 (1.07 g, 28.1 mmol, 1.00 eq) in Et_2O (40.0 mL) at room temperature and the mixture was stirred for 15 min. The solids produced were removed by cannula filtration and THF (18.0 mL, 222 mmol, 7.90 eq) was added slowly *via* syringe. The

flask was stored in the freezer for 16 h to give complete crystallisation. The solvent was removed by cannula filtration and the solid was dried under high vacuum for 7 h to give **211** (19.2 g, 71 %) as a white powder; hydrolysis of a nominal 630 μmol sample evolved 640 μmol H_2 .

(*E*)-Stilbene **210**

A Schlenk tube was charged with $\text{HAlCl}_2 \cdot 2\text{THF}$ (503 mg, 2.07 mmol, 1.51 eq) in the glove box. Under argon, Cp_2TiCl_2 (16.8 mg, 67.0 μmol , 4.89 mol%), dry toluene (2.00 mL) and phenylacetylene (151 μL , 1.37 mmol, 1.00 eq) were added and the reaction mixture was stirred at reflux for 3 h, then removed from the heat. Solid XPhos (16.6 mg, 34.8 μmol , 2.54 mol%), $\text{Pd}(\text{dba})_2$ (15.7 mg, 27.3 μmol , 1.99 mol%) were added, followed by bromobenzene (144 μL , 1.37 mmol, 1.00 eq). The reaction mixture was heated at reflux for 2 h. Aqueous 2 M HCl (3 mL) was added, the layers were separated and the aqueous phase was extracted with pentane (3 x 5 mL). The combined organic extracts were filtered through a plug of Celite[®] and SiO_2 layers and the plug was washed with pentane (5 mL). The resulting solution was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (solid load; pentane 1.05 L; pentane/ Et_2O 9:1, 0.4 L) gave **210** (25.1 mg, 10 %) as white needles, R_F (pentane) 0.30; ^1H NMR (400 MHz, CDCl_3) δ : 7.56-7.50 (m, 4H, Ar), 7.41-7.35 (m, 4H, Ar), 7.32-7.26 (m, 2H, Ar), 7.14 (s, 2H, $\text{CH}=\text{CH}$); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 137.3 (Ar), 128.7 (2C, $\text{CH}=\text{CH}$), 127.6 (Ar), 126.5 (Ar). Data were consistent with literature values.¹⁷⁷

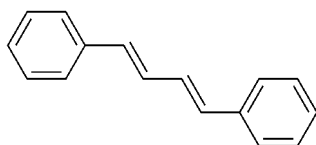
Diethyl benzylphosphonate **212**



Benzyl bromide (600 μL , 5.04 mmol, 1.00 eq) was dissolved in dry toluene (1.45 mL) under argon. Triethyl phosphite (880 μL , 5.13 mmol, 1.02 eq) was added and the reaction mixture was stirred at 120 $^\circ\text{C}$ for 5 h. The reaction mixture was cooled to room temperature and the solvent was evaporated under

reduced pressure to give the crude product. Purification by flash column chromatography (EtOAc, 0.6 L) gave **212** (1.14 g, quantitative) as a colourless oil, R_F (EtOAc) 0.38; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.34-7.22 (m, 5H, Ar), 4.06-3.96 (m, 4H, 2 x OCH_2CH_3), 3.16 (d, 2H, $J_{\text{HP}} = 21.6$ Hz, PCH_2), 1.24 (t, 6H, $J = 7.1$ Hz, 2 x CH_3); $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ : 131.6 (d, $^2J_{\text{CP}} = 9.2$ Hz, Ar), 129.8 (d, $^3J_{\text{CP}} = 6.9$ Hz, Ar), 128.5 (d, $^4J_{\text{CP}} = 3.1$ Hz, Ar), 126.8 (d, $^5J_{\text{CP}} = 3.1$ Hz, Ar), 62.1 (d, $^2J_{\text{CP}} = 6.9$ Hz, CH_2CH_3), 33.8 (d, $^1J_{\text{CP}} = 138.0$ Hz, PCH_2), 16.3 (d, $^3J_{\text{CP}} = 6.1$ Hz, CH_3). Data were consistent with literature values.¹³⁰

(*E,E*)-1,4-Diphenyl-1,3-butadiene 213



(*E*)-Cinnamaldehyde (500 μL , 3.97 mmol, 1.00 eq) was added to a 10 % $\text{K}_2\text{CO}_{3(\text{aq})}$ (6.00 mL) with vigorous stirring for 1 min before the layers were allowed to separate. In a round-bottomed flask under argon, benzyltriphenylphosphonium chloride (1.54 g, 3.97 mmol, 1.00 eq) was suspended in CH_2Cl_2 (3.00 mL) and the cinnamaldehyde mixture was added, followed by CH_2Cl_2 (1.50 mL) and 10 % $\text{NaOH}_{(\text{aq})}$ (10.0 mL). The mixture was vigorously stirred for 30 min, after which time TLC showed full consumption of cinnamaldehyde. The reaction mixture was transferred to a separating funnel, washing the flask with CH_2Cl_2 (2 x 4 mL) and H_2O (3 mL). The layers were separated and the organic phase was dried (MgSO_4) and evaporated under reduced pressure. The resulting residue was triturated with hot petrol (3 x 25 mL) until no further product was extracted, and the solvent was removed *in vacuo* to give the crude product. Under argon, petrol (10 mL) and one crystal of iodine were added. The mixture was heated at reflux for 1 h then allowed to cool to room temperature. The mixture was decolourised with 10 % $\text{Na}_2\text{S}_2\text{O}_{5(\text{aq})}$ (10 mL) and Et_2O (10 mL) was added. The layers were separated and MeOH (10 mL) was added to the organic phase. Water was added dropwise until two layers formed, and then the layers were separated. Diethyl ether was added to the petrol layer in an effort to dissolve insoluble material; this remained and was removed by filtration. The solvent was

removed under reduced pressure and the resulting white crystals were recrystallised (heptane), filtering through a Pasteur pipette of Celite[®]. Drying under high vacuum for 30 min yielded **213** (231 mg, 28 %) as a white crystalline solid, ¹H NMR (400 MHz, CDCl₃) δ: 7.48-7.43 (m, 4H, Ar), 7.38-7.31 (m, 4H, Ar), 7.27-7.22 (m, 2H, Ar), 7.02-6.92 (m, 2H, CH=CH), 6.74-6.64 (m, 2H, CH=CH). Data were consistent with literature values.¹⁷⁸

General procedure 14: Optimisation of Hydroalumination-Cross-Coupling in Toluene

(*E*)-stilbene 210

A carousel tube was charged with HAICl₂·2THF (500 mg, 2.06 mmol, 2.10 eq) in the glove box. Under argon, Cp₂TiCl₂ (17.2 mg, 69.0 μmol, 7.04 mol%), dry toluene (2.00 mL) and phenylacetylene (151 μL, 1.37 mmol, 1.40 eq) were added and the reaction mixture was stirred at reflux for 2.5 h, and then removed from the heat. Phosphine ligand (39.2 μmol, 4.00 mol%), Pd₂(dba)₃·CHCl₃ (14.7 μmol, 1.50 mol%) and DABCO (77.0 mg, 686 μmol, 70.0 mol%) were added, followed by bromobenzene (103 μL, 977 μmol, 1.00 eq). The reaction mixture was heated at reflux for 2 h. Aqueous 2 M HCl (3 mL) was added and the reaction mixture was allowed to cool to room temperature. The layers were separated and the aqueous phase was extracted with pentane (3 x 5 mL). The combined organic extracts were filtered through a plug of Celite[®] and SiO₂ layers and the plug was washed with pentane (5 mL). Tridecane (200 μL) was added, and 5 drops of the solution were diluted with Et₂O (1 mL) for GC analysis. The results are shown in **Table 17**.

General Procedure 15: Hydroalumination of Phenylacetylene

A carousel tube was charged with HAICl₂·2THF (500 mg, 2.06 mmol, 1.50 eq) in the glove box. Under argon, metallocene catalyst (70.0 μmol, 5.00 mol%), dry solvent (2.00 mL) and phenylacetylene (151 μL, 1.37 mmol, 1.00 eq) were added and the reaction mixture was stirred at reflux, taking 50 μL samples after a given time for GC analysis. The results are shown in **Tables 18 and 20**.

General Procedure 16A: Cp_2TiCl_2 -catalysed Hydroalumination-Cross-Coupling in Toluene – Method A

A carousel tube was charged with $\text{HAlCl}_2 \cdot 2\text{THF}$ (4.20 mmol, 2.10 eq) in the glove box. Under argon, Cp_2TiCl_2 (140 μmol , 7.00 mol%), dry, degassed toluene (4.00 mL) and alkyne (2.80 mmol, 1.40 eq) were added and the reaction mixture was stirred at reflux for 1 h, and then removed from the heat. Solid XPhos (80.0 μmol , 4.00 mol%), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (30.0 μmol , 1.50 mol%) and DABCO (1.40 mmol, 70.0 mol%) were dissolved in toluene (4.00 mL) and added *via* cannula, followed by aryl halide (2.00 mmol, 1.00 eq). The reaction mixture was heated at 80 °C for 2 h. Aqueous 2 M HCl (6 mL) was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (solid load).

General Procedure 16B: Cp_2TiCl_2 -catalysed Hydroalumination-Cross-Coupling in Toluene – Method B

General Procedure **16A** was followed to obtain the crude product. The crude product was redissolved in CH_2Cl_2 (5 mL) and filtered through a small plug of SiO_2 . The plug was washed with CH_2Cl_2 (2 x 5 mL) and the solvent was evaporated under reduced pressure. The residue was redissolved in 2:1 pentane/ CH_2Cl_2 (5 mL), filtration was repeated, washing with 2:1 pentane/ CH_2Cl_2 (3 x 5 mL), and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography.

General Procedure 16C: Cp_2TiCl_2 -catalysed Hydroalumination-Cross-Coupling in Toluene – Method C

General Procedure **16A** was followed until the reaction was quenched. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were filtered through a plug of SiO_2 , washing with CH_2Cl_2 (3 x 5 mL), and tridecane (400 μL) was added. An aliquot (20 drops) was diluted with Et_2O (1 mL) and analysed by GC.

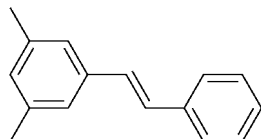
(*E*)-stilbene **210**

Using General Procedure **16A**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.03 g, 4.22 mmol), Cp_2TiCl_2 (34.6 mg, 139 μmol), phenylacetylene (310 μL , 2.80 mmol), XPhos (38.6 mg, 81.0 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (31.2 mg, 30.1 μmol), DABCO (156 mg, 1.39 mmol) and bromobenzene (210 μL , 2.00 mmol), and column chromatography (pentane 1.1 L; CH_2Cl_2 0.2 L) gave **210** (149 mg, 41 %) as a white crystalline solid. Data as above.

(*E*)-stilbene **210**

Using General Procedure **16A**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.19 mmol), Cp_2TiCl_2 (35.4 mg, 142 μmol), phenylacetylene (310 μL , 2.80 mmol), XPhos (38.2 mg, 80.1 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (31.2 mg, 30.1 μmol), DABCO (158 mg, 1.41 mmol) and bromobenzene (210 μL , 2.00 mmol) gave the crude product. The crude product was redissolved in CH_2Cl_2 (5 mL) and filtered through a small plug of SiO_2 . The plug was washed with CH_2Cl_2 (2 x 5 mL) and the solvent was evaporated under reduced pressure. The residue was redissolved in 2:1 pentane/ CH_2Cl_2 (5 mL), filtration was repeated, washing with 2:1 pentane/ CH_2Cl_2 (3 x 5 mL), and the solvent was evaporated under reduced pressure. The residue was again redissolved in 2:1 pentane/ CH_2Cl_2 (5 mL), filtration was repeated, washing with 2:1 pentane/ CH_2Cl_2 (3 x 5 mL), and the solvent was evaporated under reduced pressure to give **210** (197 mg, 55 %) as a yellow granular solid. Data as above.

(*E*)-1,3-dimethyl-5-styrylbenzene **257**



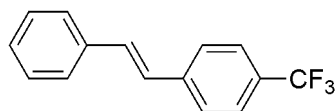
Using General Procedure **16B**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.20 mmol), Cp_2TiCl_2 (34.6 mg, 139 μmol), phenylacetylene (310 μL , 2.80 mmol), XPhos (37.9 mg, 79.5 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (30.8 mg, 29.8 μmol), DABCO (156 mg, 1.39 mmol) and 5-bromo-*m*-xylene (270 μL , 2.00 mmol), and column chromatography (pentane 1.0 L) gave **257** (116 mg, 28 %) as a colourless oil, R_F (pentane) 0.25; ^1H NMR (400 MHz, CDCl_3) δ : 7.52 (d, 2H, $J = 7.5$ Hz, Ar), 7.37 (t, 2H, $J = 7.6$ Hz, Ar), 7.30-7.24 (m, 1H, Ar), 7.16 (s, 2H, Ar), 7.10 (s,

1H, Ar) overlapped by 7.08 (s, 1H, PhCH), 6.93 (s, 1H, PhCH=CH), 2.36 (s, 6H, 2 x CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ: 138.1 (CH₃C), 137.5 (Ar), 137.2 (Ar), 129.4 (PhCH=CH), 128.9 (Ar), 128.6 (Ar), 128.3 (Ar), 127.4 (PhCH), 126.4 (Ar), 124.4 (Ar), 21.3 (2 x CH₃). Data were consistent with those in the literature.¹⁷⁹

(E)-1,3-dimethyl-5-styrylbenzene **257**

Using General Procedure **16C**, HAlCl₂·2THF (1.03 g, 4.23 mmol), Cp₂TiCl₂ (34.2 mg, 137 μmol), phenylacetylene (310 μL, 2.80 mmol), XPhos (38.0 mg, 79.7 μmol), Pd₂(dba)₃·CHCl₃ (31.5 mg, 30.4 μmol), DABCO (158 mg, 1.40 mmol) and 5-bromo-*m*-xylene (270 μL, 2.00 mmol) gave **257** (1.30 mmol, 65 %) by GC.

(E)-4-Trifluoromethylstilbene **258**



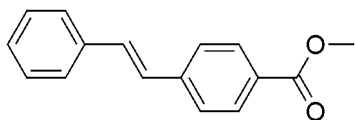
Using General Procedure **16B**, HAlCl₂·2THF (1.02 g, 4.20 mmol), Cp₂TiCl₂ (35.0 mg, 141 μmol), phenylacetylene (310 μL, 2.80 mmol), XPhos (38.2 mg, 80.1 μmol), Pd₂(dba)₃·CHCl₃ (30.8 mg, 29.8 μmol), DABCO (157 mg, 1.40 mmol) and 4-bromobenzotrifluoride (280 μL, 2.00 mmol), and column chromatography (pentane 1.0 L) gave **258** (237 mg, 48 %) as a white crystalline solid, *R*_F (pentane) 0.44; ¹H NMR (400 MHz, CDCl₃) δ: 7.62 (s, 4H, Ar), 7.57-7.53 (m, 2H, Ar), 7.43-7.37 (m, 2H, Ar), 7.34-7.29 (m, 1H, Ar), 7.21 (d, 1H, *J* = 16.4 Hz, CH=CH), 7.13 (d, 1H, *J* = 16.4 Hz, CH=CH); ¹³C NMR (100.6 MHz, CDCl₃) δ: 140.8 (Ar), 136.6 (Ar), 131.2 (CH=CH), 129.2 (q, ²*J*_{CF} = 33.0 Hz, Ar), 128.8 (Ar), 128.3 (Ar), 127.1 (CH=CH), 126.8 (Ar), 126.5 (Ar), 125.6 (q, ³*J*_{CF} = 3.8 Hz, Ar), 124.2 (q, ¹*J*_{CF} = 271.4 Hz, CF₃); ¹⁹F NMR (376.5 MHz, CDCl₃) δ: -62.43 (s). Data were consistent with those in the literature.¹⁸⁰

(E)-4-Trifluoromethylstilbene **258**

Using General Procedure **16C**, HAlCl₂·2THF (1.03 g, 4.24 mmol), Cp₂TiCl₂ (35.5 mg, 143 μmol), phenylacetylene (310 μL, 2.80 mmol), XPhos (37.7 mg,

79.1 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (31.3 mg, 30.2 μmol), DABCO (161 mg, 1.43 mmol) and 4-bromobenzotrifluoride (280 μL , 2.00 mmol) gave **258** (1.39 mmol, 70 %) by GC.

Methyl 4-[(*E*)-2-phenylethenyl]benzoate **259**

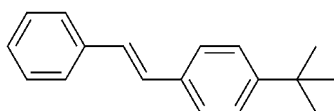


Using General Procedure **16A**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.18 mmol), Cp_2TiCl_2 (34.6 mg, 139 μmol), phenylacetylene (310 μL , 2.80 mmol), XPhos (38.7 mg, 81.2 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (30.9 mg, 29.9 μmol), DABCO (158 mg, 1.41 mmol) and methyl 4-bromobenzoate (430 mg, 2.00 mmol) gave the crude product. The crude product was redissolved in CH_2Cl_2 (5 mL) and filtered through a small plug of SiO_2 . The plug was washed with CH_2Cl_2 (2 x 5 mL) and the solvent was evaporated under reduced pressure. The residue was redissolved in 2:1 pentane/ CH_2Cl_2 (5 mL), filtration was repeated, washing with 2:1 pentane/ CH_2Cl_2 (3 x 5 mL), and the solvent was evaporated under reduced pressure. The plug was washed with CH_2Cl_2 (2 x 10 mL), and the solvent was evaporated under reduced pressure to give **259** (204 mg, 43 %) as a buff crystalline solid, ^1H NMR (400 MHz, CDCl_3) δ : 8.04 (dt, 2H, J = 8.4, 1.8 Hz, Ar), 7.61-7.52 (m, 4H, Ar), 7.42-7.36 (m, 2H, Ar), 7.34-7.28 (m, 1H, Ar), 7.23 (d, 1H, J = 16.3 Hz, CH=CH), 7.14 (d, 1H, J = 16.3 Hz, CH=CH), 3.94 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 166.9 (ArCO), 141.8 (Ar), 136.7 (Ar), 131.2 (CH=CH), 130.0 (Ar), 128.9 (Ar), 128.8 (Ar), 128.2 (CH=CH), 127.5 (Ar), 126.8 (Ar), 126.3 (Ar), 52.1 (CH_3). Data were consistent with those in the literature.¹⁸¹

Methyl 4-[(*E*)-2-phenylethenyl]benzoate **259**

Using General Procedure **16C**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.20 mmol), Cp_2TiCl_2 (34.8 mg, 140 μmol), phenylacetylene (310 μL , 2.80 mmol), XPhos (38.4 mg, 80.5 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (31.6 mg, 30.5 μmol), DABCO (162 mg, 1.44 mmol) and methyl 4-bromobenzoate (433 mg, 2.01 mmol) gave **259** (1.36 mmol, 68 %) by GC.

(*E*)-4-*tert*-Butylstilbene **260**

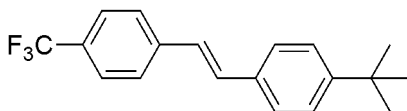


Using General Procedure **16B**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.03 g, 4.24 mmol), Cp_2TiCl_2 (35.0 mg, 141 μmol), 4-*tert*-butylphenylacetylene (510 μL , 2.80 mmol), XPhos (37.6 mg, 78.9 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (31.7 mg, 30.6 μmol), DABCO (156 mg, 1.39 mmol) and bromobenzene (210 μL , 2.00 mmol), and column chromatography (pentane 1.0 L) gave **260** (160 mg, 34 %) as a white crystalline solid, R_F (pentane) 0.24; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.55-7.51 (m, 2H, Ar), 7.50-7.46 (m, 2H, Ar), 7.43-7.34 (m, 4H, Ar), 7.29-7.24 (m, 1H, Ar), 7.13 (d, 1H, $J = 16.4$ Hz, $\text{CH}=\text{CH}$), 7.08 (d, 1H, $J = 16.4$ Hz, $\text{CH}=\text{CH}$), 1.35 (s, 9H, $\text{C}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ : 150.8 (Ar), 137.5 (Ar), 134.5 (Ar), 128.6 (Ar), 128.5 ($\text{CH}=\text{CH}$), 127.9 ($\text{CH}=\text{CH}$), 127.4 (Ar), 126.4 (Ar), 126.2 (Ar), 125.6 (Ar), 34.6 ($\text{C}(\text{CH}_3)_3$), 31.3 ($\text{C}(\text{CH}_3)_3$). Data were consistent with those in the literature.¹⁸²

(*E*)-4-*tert*-Butylstilbene **260**

Using General Procedure **16C**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.20 mmol), Cp_2TiCl_2 (34.9 mg, 140 μmol), 4-*tert*-butylphenylacetylene (510 μL , 2.80 mmol), XPhos (37.8 mg, 79.3 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (30.8 mg, 29.8 μmol), DABCO (156 mg, 1.39 mmol) and bromobenzene (210 μL , 2.00 mmol) gave **260** (1.44 mmol, 72 %) by GC.

(*E*)-1-*tert*-butyl-4-(4-(trifluoromethyl)styryl)benzene **261**



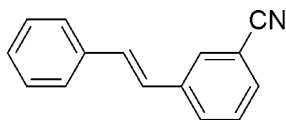
Using General Procedure **16B**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.21 mmol), Cp_2TiCl_2 (34.1 mg, 137 μmol), 4-*tert*-butylphenylacetylene (510 μL , 2.80 mmol), XPhos (38.6 mg, 81.0 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (30.6 mg, 29.6 μmol), DABCO (156 mg, 1.39 mmol) and 4-bromobenzotrifluoride (280 μL , 2.00 mmol), and column chromatography (pentane 1.1 L) gave **261** (138 mg, 23 %) as a white powder, mp 112-114 $^\circ\text{C}$; R_F (pentane) 0.26; IR (CHCl_3) 3055, 1615, 1325, 1168, 1127, 1067 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.67-7.59 (m, 4H, Ar),

7.52 (d, 2H, $J = 8.6$ Hz, Ar), 7.46 (d, 2H, $J = 8.6$ Hz, Ar), 7.23 (d, 1H, $J = 16.4$ Hz, CH=CH), 7.12 (d, 1H, $J = 16.4$ Hz, CH=CH), 1.40 (s, 9H, 3 x CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ: 151.6 (Ar), 141.0 (Ar), 133.9 (Ar), 131.0 (CH=CH), 129.0 (q, ²J_{CF} = 32.2 Hz, Ar), 126.5 (Ar), 126.4 (Ar), 126.3 (CH=CH), 125.7 (Ar), 125.6 (q, ³J_{CF} = 3.8 Hz, Ar), 124.3 (q, ¹J_{CF} = 271.4 Hz, CF₃), 34.7 (ArC(CH₃)₃), 31.2 (ArC(CH₃)₃); ¹⁹F NMR (376.5 MHz, CDCl₃) δ: -62.34 (s); HRMS (EI), m/z for C₁₉H₁₉F₃ (M⁺), calcd. 304.1439, found 304.1447.

(E)-1-tert-butyl-4-(4-(trifluoromethyl)styryl)benzene 261

Using General Procedure **16C**, HAlCl₂·2THF (1.02 g, 4.21 mmol), Cp₂TiCl₂ (35.3 mg, 142 μmol), 4-tert-butylphenylacetylene (510 μL, 2.80 mmol), XPhos (38.0 mg, 79.7 μmol), Pd₂(dba)₃·CHCl₃ (30.8 mg, 29.8 μmol), DABCO (162 mg, 1.45 mmol) and 4-bromobenzotrifluoride (280 μL, 2.00 mmol) gave **261** (1.48 mmol, 74 %) by GC.

(E)-3-cyanostilbene 262

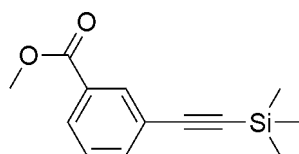


Using General Procedure **16B**, HAlCl₂·2THF (1.04 g, 4.27 mmol), Cp₂TiCl₂ (34.4 mg, 138 μmol), phenylacetylene (310 μL, 2.80 mmol), XPhos (38.4 mg, 80.5 μmol), Pd₂(dba)₃·CHCl₃ (31.4 mg, 30.3 μmol), DABCO (156 mg, 1.39 mmol) and 3-bromobenzonitrile (365 mg, 2.00 mmol), and column chromatography (pentane/Et₂O 19:1, 1.2 L) gave **262** (105 mg, 25 %) as a yellow solid, R_F (pentane/Et₂O 19:1) 0.15; ¹H NMR (400 MHz, CDCl₃) δ: 7.80-7.77 (m, 1H, Ar), 7.73 (d, 1H, $J = 7.8$ Hz, Ar), 7.56-7.51 (m, 3H, Ar), 7.47 (t, 1H, $J = 7.8$ Hz, Ar), 7.43-7.37 (m, 2H, Ar), 7.36-7.30 (m, 1H, Ar), 7.17 (d, 1H, $J = 16.3$ Hz, CH=CH), 7.07 (d, 1H, $J = 16.3$ Hz, CH=CH); ¹³C NMR (100.6 MHz, CDCl₃) δ: 138.6 (Ar), 136.3 (Ar), 131.3 (Ar), 130.7 (Ar), 130.5 (Ar), 129.8 (Ar), 129.4 (Ar), 128.8 (Ar), 128.4 (CH=CH), 126.8 (Ar), 126.2 (CH=CH), 118.8 (CN), 112.9 (Ar). Data were consistent with those in the literature.¹⁸³

(E)-stilbene 210

A carousel tube was charged with $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.01 g, 4.16 mmol, 2.08 eq) in the glove box. Under argon, Cp_2TiCl_2 (34.1 mg, 137 μmol , 6.85 mol%), toluene (4.00 mL) and phenylacetylene (310 μL , 2.80 mmol, 1.40 eq) were added and the reaction mixture was stirred at reflux for 1 h, and then removed from the heat. XPhos (38.0 mg, 79.7 μmol , 3.99 mol%), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (30.6 mg, 29.6 μmol , 1.48 mol%) and DABCO (154 mg, 1.37 mmol, 68.5 mol%) were dissolved in toluene (4.00 mL) and transferred to the reaction mixture *via* cannula, followed by bromobenzene (210 μL , 2.00 mmol, 1.00 eq). The reaction mixture was heated at 80 °C for 2 h. Aqueous 2 M Rochelle's salt solution (6 mL) was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were evaporated under reduced pressure to give the crude product. The crude product was redissolved in CH_2Cl_2 (5 mL) and filtered through a small plug of SiO_2 . The plug was washed with CH_2Cl_2 (3 x 5 mL) and the solvent was evaporated under reduced pressure. The residue was redissolved in 2:1 pentane/ CH_2Cl_2 (5 mL), filtration was repeated, washing with 2:1 pentane/ CH_2Cl_2 (3 x 5 mL), and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (solid load; pentane 1.5 L; CH_2Cl_2 0.2 L) to give **210** (134 mg, 37 %). Data as above.

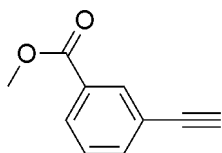
Methyl 3-((trimethylsilyl)ethynyl)benzoate 214



Methyl 3-bromobenzoate (3.01 g, 14.0 mmol, 1.00 eq) was dissolved in freshly distilled MeCN (70.0 mL) under argon. Solid $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (198 mg, 282 μmol , 2.01 mol%) and CuI (27.8 mg, 146 μmol , 1.04 mol%) were added, followed by Et_3N (3.90 mL, 28.0 mmol, 2.00 eq) and trimethylsilylacetylene (2.30 mL, 16.8 mmol, 1.20 eq). The mixture was stirred at 50 °C for 24 h. The solvent was removed under reduced pressure to give the crude product as a dark brown/black residue. The residue was filtered through a plug of Celite® to remove residual Pd, washing with pentane (4 x 20 mL) then CH_2Cl_2 (4 x

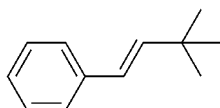
20 mL). The solvent was removed *in vacuo*. Purification by flash column chromatography (hexane/EtOAc 80:1, 2.0 L) gave a 73:27 mixture of **214** and aryl bromide starting material as an orange crystalline solid (2.96 g, 91 %). Data for **214**: R_F (hexane/EtOAc 80:1) 0.07; 1H NMR (400 MHz, $CDCl_3$) δ : 8.14 (t, 1H, $J = 1.6$ Hz, Ar), 8.00-7.95 (m, 1H, Ar), 7.64 (dt, 1H, $J = 7.7, 1.4$ Hz, Ar), 7.38 (t, 1H, $J = 7.7$ Hz, Ar), 3.92 (s, 3H, CO_2CH_3), 0.26 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 166.3 (C=O), 136.0 (Ar), 133.1 (Ar), 130.3 (Ar), 129.4 (Ar), 128.3 (Ar), 123.6 (Ar), 103.8 (CC), 95.3 (CC), 52.2 (CO_2CH_3), -0.2 ($SiCH_3$). Data were consistent with literature values.¹⁸⁴ The mixture was used without further purification (9.30 mmol desired product).

Methyl 3-ethynylbenzoate **215**



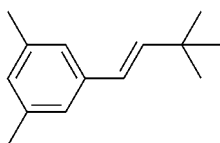
Methyl 3-((trimethylsilyl)ethynyl)benzoate **214** (2.96 g, 9.30 mmol based on 73 % purity, 1.00 eq) was dissolved in THF (70.0 mL) under argon, and TBAF (6.58 g, 25.2 mmol, 2.70 eq) was added. The mixture was stirred at room temperature for 1 h. Saturated $NH_4Cl_{(aq)}$ solution (70 mL) was added and the mixture was extracted with EtOAc (3 x 60 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (solid load; hexane/EtOAc 4:1, 2.0 L) gave **215** (1.05 g, 70 %) as a pale yellow solid, R_F (hexane/EtOAc 4:1) 0.48; 1H NMR (400 MHz, $CDCl_3$) δ : 8.17 (t, 1H, $J = 1.4$ Hz, Ar), 8.02 (dt, 1H, $J = 7.8, 1.4$ Hz, Ar), 7.67 (dt, 1H, $J = 7.8, 1.4$ Hz, Ar), 7.41 (t, 1H, $J = 7.8$ Hz, Ar), 3.93 (s, 3H, CH_3), 3.13 (s, 1H, $ArCCH$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 166.2 (C=O), 136.2 (Ar), 133.2 (Ar), 130.4 (Ar), 129.8 (Ar), 128.5 (Ar), 122.6 (Ar), 82.5 (CC), 78.1 (CC), 52.3 (CO_2CH_3). Data were consistent with literature values.¹⁸⁴

(E)-3,3-Dimethyl-1-phenylbut-1-ene 263



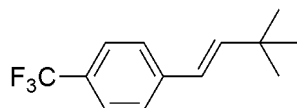
Using General Procedure **16A**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.20 mmol), Cp_2TiCl_2 (35.2 mg, 141 μmol), 3,3-dimethyl-1-butyne (350 μL , 2.80 mmol), XPhos (38.3 mg, 80.3 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (30.9 mg, 29.9 μmol), DABCO (159 mg, 1.42 mmol) and bromobenzene (210 μL , 2.00 mmol), with column chromatography using pentane (0.7 L) as eluent, afforded **263** (215 mg, 67 %) as a pale yellow oil, R_F (pentane) 0.68; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.39 (d, 2H, $J = 7.6$ Hz, Ar), 7.32 (t, 2H, $J = 7.6$ Hz, Ar), 7.21 (t, 1H, $J = 7.3$ Hz, Ar), 6.34 (d, 1H, $J = 16.2$ Hz, CH), 6.28 (d, 1H, $J = 16.2$ Hz, CH), 1.15 (s, 9H, 3 x CH_3); $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ : 141.8 (ArCH=CH), 138.1 (Ar), 128.5 (Ar), 126.7 (ArCH), 126.0 (Ar), 124.6 (Ar), 33.3 ($\text{C}(\text{CH}_3)_3$), 29.6 (3 x CH_3). Data were consistent with literature values.¹⁸⁵

(E)-1-(3,3-Dimethylbut-1-enyl)-3,5-dimethylbenzene 264



Using General Procedure **16A**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.18 mmol), Cp_2TiCl_2 (34.6 mg, 139 μmol), 3,3-dimethyl-1-butyne (350 μL , 2.80 mmol), XPhos (38.2 mg, 80.1 μmol), $\text{Pd}(\text{dba})_2$ (34.2 mg, 59.5 μmol), DABCO (156 mg, 1.39 mmol) and 5-bromo-*m*-xylene (270 μL , 2.00 mmol), with column chromatography using pentane (0.6 L) as eluent, afforded **264** (190 mg, 50 %) as a pale yellow oil, R_F (pentane) 0.63; IR (CHCl_3) 3010, 2962, 2866, 1600, 1477, 1463, 1391, 1272, 1259 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.04 (s, 2H, Ar), 6.89 (s, 1H, Ar), 6.30-6.28 (m, 2H, CH=CH), 2.36-2.33 (m, 6H, 2 x Ar CH_3), 1.19-1.13 (m, 9H, RC(CH_3)₃); $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ : 141.5 (Ar), 137.9 (Ar), 137.9 (CH=CH), 128.4 (Ar), 124.6 (CH=CH), 123.9 (Ar), 33.3 (RC(CH_3)₃), 29.6 (RC(CH_3)₃), 21.3 (Ar CH_3); HRMS (EI), m/z for $\text{C}_{14}\text{H}_{20}$ (M^+), calcd. 188.1565, found 188.1566.

(E)-1-(3,3-Dimethylbut-1-enyl)-4-(trifluoromethyl)benzene 265

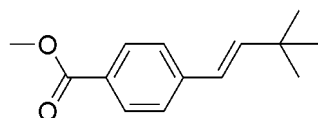


Using General Procedure **16A**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.19 mmol), Cp_2TiCl_2 (34.3 mg, 138 μmol), 3,3-dimethyl-1-butyne (350 μL , 2.80 mmol), XPhos (38.3 mg, 80.3 μmol), $\text{Pd}(\text{dba})_2$ (34.4 mg, 59.8 μmol), DABCO (160 mg, 1.43 mmol) and 4-bromobenzotrifluoride (280 μL , 2.00 mmol), with column chromatography using pentane (0.6 L) as eluent, afforded **265** (359 mg, 79 %) as a colourless oil, R_F (pentane) 0.65; **IR** (CHCl_3) 2963, 1616, 1326, 1167, 1127, 1068 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ : 7.55 (d, 2H, $J = 8.3$ Hz, Ar), 7.46 (d, 2H, $J = 8.3$ Hz, Ar), 6.38 (d, 1H, $J = 16.2$ Hz, $\text{CH}=\text{CH}$), 6.33 (d, 1H, $J = 16.2$ Hz, $\text{CH}=\text{CH}$), 1.15 (s, 9H, 3 x CH_3); **^{13}C NMR** (100.6 MHz, CDCl_3) δ : 144.6 ($\text{CH}=\text{CH}$), 141.6 (Ar), 128.6 (q, $^2J_{\text{CF}} = 32.2$ Hz, Ar), 126.1 (Ar), 125.4 (q, $J_{\text{CF}} = 3.8$ Hz, Ar), 124.3 (q, $^1J_{\text{CF}} = 271.4$ Hz, CF_3), 123.6 ($\text{CH}=\text{CH}$), 33.6 ($\text{RC}(\text{CH}_3)_3$), 29.4 ($\text{RC}(\text{CH}_3)_3$); **^{19}F NMR** (376.5 MHz, CDCl_3) δ : -62.34 (s); **HRMS** (EI), m/z for $\text{C}_{13}\text{H}_{15}\text{F}_3$ (M^+), calcd. 228.1126, found 228.1126. Data were consistent with literature values.¹⁸⁶

(E)-1-(3,3-Dimethylbut-1-enyl)-4-(trifluoromethyl)benzene 265

Using General Procedure **16C**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.24 mmol), Cp_2TiCl_2 (34.9 mg, 140 μmol), 3,3-dimethyl-1-butyne (350 μL , 2.80 mmol), XPhos (38.4 mg, 80.5 μmol), $\text{Pd}(\text{dba})_2$ (34.7 mg, 60.3 μmol), DABCO (160 mg, 1.42 mmol) and 4-bromobenzotrifluoride (280 μL , 2.00 mmol) gave **265** (1.50 mmol, 75 %) by GC.

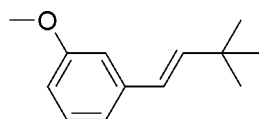
(E)-Methyl 4-(3,3-dimethylbut-1-enyl)benzoate 266



Using General Procedure **16A**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.18 mmol), Cp_2TiCl_2 (35.2 mg, 141 μmol), 3,3-dimethyl-1-butyne (350 μL , 2.80 mmol), XPhos (37.8 mg, 79.3 μmol), $\text{Pd}(\text{dba})_2$ (34.2 mg, 59.4 μmol), DABCO (158 mg, 1.41 mmol) and methyl 4-bromobenzoate (433 mg, 2.01 mmol), with column chromatography using pentane/ Et_2O 19:1 (0.8 L) as eluent, afforded **266**

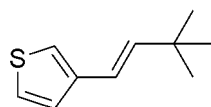
(344 mg, 78 %) as a pearlescent solid, **mp** 38-40 °C; **R_F** (pentane/Et₂O 19:1) 0.51; **IR** (CHCl₃) 2963, 1716, 1608, 1437, 1285, 1179, 1112 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 7.97 (d, 2H, *J* = 8.4 Hz, Ar), 7.42 (d, 2H, *J* = 8.4 Hz, Ar), 6.40 (d, 1H, *J* = 16.2 Hz, CH=CH), 6.34 (d, 1H, *J* = 16.2 Hz, CH=CH), 3.91 (s, 3H, OCH₃), 1.14 (s, 9H, RC(CH₃)₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 167.0 (C=O), 144.6 (CH=CH), 142.6 (Ar), 129.8 (Ar), 128.2 (Ar), 125.9 (Ar), 124.0 (CH=CH), 52.0 (OCH₃), 33.6 (RC(CH₃)₃), 29.4 (RC(CH₃)₃); **HRMS** (EI), *m/z* for C₁₄H₁₈O₂ (M⁺), calcd. 218.1307, found 218.1306. Reported in the literature without spectroscopic data.¹⁸⁷

(*E*)-3-(3,3-Dimethylbut-1-enyl)anisole 267



Using General Procedure **16A**, HAlCl₂·2THF (1.02 g, 4.21 mmol), Cp₂TiCl₂ (35.3 mg, 142 μmol), 3,3-dimethyl-1-butyne (350 μL, 2.80 mmol), XPhos (37.9 mg, 79.5 μmol), Pd₂(dba)₃·CHCl₃ (30.8 mg, 29.8 μmol), DABCO (157 mg, 1.40 mmol) and 3-bromoanisole (250 μL, 2.00 mmol), with column chromatography using pentane/Et₂O 40:1 (0.82 L) as eluent, afforded **267** (325 mg, 85 %) as a pale yellow oil, **R_F** (pentane/Et₂O 40:1) 0.49; **IR** (CHCl₃) 3012, 2962, 1598, 1579, 1465, 1364, 1247, 1157, 1051 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ: 7.24 (t, 1H, *J* = 7.9 Hz, Ar), 7.00 (d, 1H, *J* = 7.9 Hz, Ar), 6.96-6.93 (m, 1H, Ar), 6.79 (dd, 1H, *J* = 8.2, 2.6 Hz, Ar), 6.35-6.26 (m, 2H, CH=CH), 3.85 (s, 3H, OCH₃), 1.16 (s, 9H, RC(CH₃)₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ: 159.8 (Ar), 142.1 (Ar), 139.5 (Ar), 129.4 (Ar), 124.5 (CH=CH), 118.7 (Ar), 112.4 (Ar), 111.3 (CH=CH), 55.2 (OCH₃), 33.3 (RC(CH₃)₃), 29.6 (RC(CH₃)₃); **HRMS** (EI), *m/z* for C₁₃H₁₈O (M⁺), calcd. 190.1358, found 190.1355.

(*E*)-3-(3,3-Dimethylbut-1-enyl)thiophene 268



Using General Procedure **16A**, HAlCl₂·2THF (1.02 g, 4.21 mmol), Cp₂TiCl₂ (35.0 mg, 141 μmol), 3,3-dimethyl-1-butyne (350 μL, 2.80 mmol), XPhos

(38.6 mg, 81.0 μmol), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (31.0 mg, 29.9 μmol), DABCO (157 mg, 1.40 mmol) and 3-bromothiophene (190 μL , 2.00 mmol), with column chromatography using pentane (0.6 L) as eluent, afforded **268** (138 mg, 41 %) as a pale yellow oil, R_F (pentane) 0.74; **IR** (CHCl_3) 2963, 1463, 1363, 1265, 969 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ : 7.27 (dd, 1H, $J = 5.1, 2.9$ Hz, *SCHCH*), 7.22 (dd, 1H, $J = 5.1, 1.0$ Hz, *SCHCH*), 7.09 (dd, 1H, $J = 2.9, 1.0$ Hz, *SCHCR*), 6.35 (d, 1H, $J = 16.1$ Hz, *CH=CH*), 6.14 (d, 1H, $J = 16.1$ Hz, *CH=CH*), 1.13 (s, 9H, 3 x CH_3); **^{13}C NMR** (100.6 MHz, CDCl_3) δ : 141.8 (*CH=CH*), 140.6 (Ar), 125.7 (Ar), 124.9 (Ar), 120.4 (*CH=CH*), 119.0 (Ar), 33.3 ($\text{RC}(\text{CH}_3)_3$), 29.6 ($\text{RC}(\text{CH}_3)_3$); **HRMS** (EI), m/z for $\text{C}_{10}\text{H}_{14}\text{S}$ (M^+), calcd. 166.0816, found 166.0814.

General Procedure 17: $\text{Cp}^*_2\text{ZrCl}_2$ -catalysed Hydroalumination-Cross-Coupling in THF

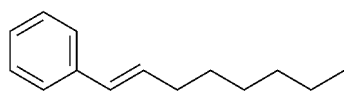
A carousel tube was charged with $\text{HAlCl}_2\cdot 2\text{THF}$ (4.20 mmol, 2.10 eq) and $\text{Cp}^*_2\text{ZrCl}_2$ (140 μmol , 7.00 mol%) in the glove box. Under argon, THF (4.00 mL) and alkyne (2.80 mmol, 1.40 eq) were added and the reaction mixture was stirred at reflux for 16 h, and then removed from the heat. In a flame-dried, stirrer-equipped Schlenk tube under argon, XPhos (80.0 μmol , 4.00 mol%), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (30.0 μmol , 1.50 mol%) and DABCO (1.40 mmol, 70.0 mol%) were dissolved in THF (4.00 mL) and transferred to the reaction mixture *via* cannula. Aryl halide (2.00 mmol, 1.00 eq) was added and the reaction mixture was heated at reflux for 2 h. Aqueous 2 M HCl (6 mL) was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (solid load).

General Procedure 18: Cp_2TiCl_2 -catalysed Hydroalumination-Cross-Coupling in THF

A carousel tube was charged with $\text{HAlCl}_2\cdot 2\text{THF}$ (4.20 mmol, 2.10 eq) in the glove box. Under argon, Cp_2TiCl_2 (140 μmol , 7.00 mol%), THF (4.00 mL) and alkyne (2.80 mmol, 1.40 eq) were added and the reaction mixture was stirred at reflux for 2 h, and then removed from the heat. In a flame-dried,

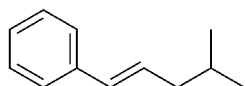
stirrer-equipped Schlenk tube under argon, XPhos (80.0 μmol , 4.00 mol%), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (30.0 μmol , 1.50 mol%) and DABCO (1.40 mmol, 70.0 mol%) were dissolved in THF (4.00 mL) and transferred to the reaction mixture *via* cannula. Aryl halide (2.00 mmol, 1.00 eq) was added and the reaction mixture was heated at reflux for 2 h. Aqueous 2 M HCl (6 mL) was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (solid load).

(*E*)-1-Phenyl-1-octene **269**



Using General Procedure **17**, $\text{HAlCl}_2\cdot 2\text{THF}$ (1.03 g, 4.22 mmol), $\text{Cp}^*_2\text{ZrCl}_2$ (64 mg, 150 μmol), 1-octyne (410 μL , 2.80 mmol), XPhos (38.2 mg, 80.1 μmol), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (31.2 mg, 30.1 μmol), DABCO (164 mg, 1.46 mmol) and bromobenzene (210 μL , 2.00 mmol) afforded **269** (367 mg, 98 %) as a colourless oil, R_F (pentane) 0.70; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.38 (d, 2H, $J = 7.9$ Hz, Ar), 7.32 (t, 2H, $J = 7.3$ Hz, Ar), 7.22 (t, 1H, $J = 7.3$ Hz, Ar), 6.41 (d, 1H, $J = 15.8$ Hz, PhCH), 6.26 (dt, 1H, $J = 15.8, 7.2$ Hz, Ar), 2.24 (q, 2H, $J = 7.2$ Hz, CHCH_2), 1.55-1.44 (m, 2H, CH_2), 1.43-1.22 (m, 6H, 3 x CH_2), 0.97-0.87 (m, 3H, CH_3); $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ : 138.0 (Ar), 131.2 (ArCH=CH), 129.7 (ArCH), 128.4 (Ar), 126.7 (Ar), 125.9 (Ar), 33.1 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 28.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3). Data were consistent with literature values.¹⁸⁸

(*E*)-4-Methyl-1-phenylpent-1-ene **270**



Using General Procedure **17**, $\text{HAlCl}_2\cdot 2\text{THF}$ (1.02 g, 4.19 mmol), $\text{Cp}^*_2\text{ZrCl}_2$ (61 mg, 140 μmol), 4-methyl-1-pentyne (330 μL , 2.80 mmol), XPhos (38.1 mg, 79.9 μmol), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (30.7 mg, 29.7 μmol), DABCO (158 mg, 1.41 mmol) and bromobenzene (210 μL , 2.00 mmol) afforded **270** (281 mg, 88 %) as a pale yellow oil, R_F (pentane) 0.64; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ :

7.42-7.13 (m, 5H, Ar), 6.37 (d, 1H, $J = 15.8$ Hz, CH), 6.27-6.15 (m, 1H, CH), 2.10 (t, 2H, $J = 6.9$ Hz, $^i\text{PrCH}_2$), 1.74 (sept, 1H, $J = 6.7$ Hz, $(\text{CH}_3)_2\text{CH}$), 0.96 (d, 6H, $J = 6.7$ Hz, 2 x CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 137.9 (Ar), 130.8 (ArCH=CH), 129.6 (ArCH), 128.4 (Ar), 126.8 (Ar), 125.9 (Ar), 42.4 (CH_2), 28.6 ($\text{CH}(\text{CH}_3)_2$), 22.4 (2 x CH_3). Data were consistent with literature values.¹⁸⁹

(E)-3,3-Dimethyl-1-phenylbut-1-ene 263

Using General Procedure **17**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.18 mmol), $\text{Cp}^*_2\text{ZrCl}_2$ (60 mg, 140 μmol), 3,3-dimethyl-1-butyne (350 μL , 2.80 mmol), XPhos (37.9 mg, 79.5 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (30.7 mg, 29.7 μmol), DABCO (158 mg, 1.40 mmol) and bromobenzene (210 μL , 2.00 mmol) afforded **263** (130 mg, 41 %) as a pale yellow oil. Data as above.

(E)-Stilbene 210

Using General Procedure **17**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.21 mmol), $\text{Cp}^*_2\text{ZrCl}_2$ (59 mg, 140 μmol), phenylacetylene (310 μL , 2.80 mmol), XPhos (38.8 mg, 81.4 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (31.2 mg, 30.1 μmol), DABCO (157 mg, 1.40 mmol) and bromobenzene (210 μL , 2.00 mmol) afforded **210** (338 mg, 94 %) as a white crystalline solid. Data as above.

(E)-1,3-Dimethyl-5-styrylbenzene 257

Using General Procedure **17**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.19 mmol), $\text{Cp}^*_2\text{ZrCl}_2$ (62 mg, 140 μmol), phenylacetylene (310 μL , 2.80 mmol), XPhos (38.0 mg, 79.7 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (30.4 mg, 29.4 μmol), DABCO (166 mg, 1.48 mmol) and 5-bromo-*m*-xylene (270 μL , 2.00 mmol) afforded **257** (231 mg, 55 %) as a colourless oil. Data as above.

(E)-3,3-Dimethyl-1-phenylbut-1-ene 263

Using General Procedure **18**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.18 mmol), Cp_2TiCl_2 (34.6 mg, 139 μmol), 3,3-dimethyl-1-butyne (350 μL , 2.80 mmol), XPhos (38.3 mg, 80.3 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (31.7 mg, 30.6 μmol), DABCO (158 mg, 1.40 mmol) and bromobenzene (210 μL , 2.00 mmol) afforded **263** (298 mg, 93 %) as a pale yellow oil. Data as above.

(E)-Stilbene 210

Using General Procedure **18**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.04 g, 4.26 mmol), Cp_2TiCl_2 (35.3 mg, 142 μmol), phenylacetylene (310 μL , 2.80 mmol), XPhos (38.2 mg, 80.1 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (31.5 mg, 30.4 μmol), DABCO (156 mg, 1.39 mmol) and bromobenzene (210 μL , 2.00 mmol) afforded **210** (339 mg, 94 %) as a white crystalline solid. Data as above.

(E)-Stilbene 210

Using General Procedure **17**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.18 mmol), $\text{Cp}^*_2\text{ZrCl}_2$ (64 mg, 150 μmol), phenylacetylene (310 μL , 2.80 mmol), XPhos (38.5 mg, 80.8 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (31.3 mg, 30.2 μmol), DABCO (162 mg, 1.44 mmol) and iodobenzene (220 μL , 2.00 mmol) afforded **210** (355 mg, 98 %) as a white crystalline solid. Data as above.

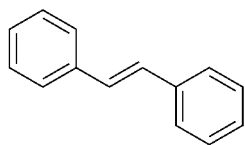
(E)-Stilbene 210

Using General Procedure **17**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.03 g, 4.24 mmol), $\text{Cp}^*_2\text{ZrCl}_2$ (61 mg, 140 μmol), phenylacetylene (310 μL , 2.80 mmol), XPhos (38.9 mg, 81.6 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (31.0 mg, 29.9 μmol), DABCO (164 mg, 1.47 mmol) and chlorobenzene (200 μL , 2.00 mmol) afforded **210** (146 mg, 40 %) as a white crystalline solid. Data as above.

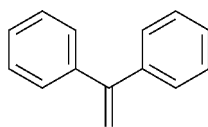
(E)-Stilbene 210

Using General Procedure **17**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.02 g, 4.21 mmol), $\text{Cp}^*_2\text{ZrCl}_2$ (59 mg, 140 μmol), phenylacetylene (310 μL , 2.80 mmol), XPhos (38.3 mg, 80.3 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (30.4 mg, 29.4 μmol), DABCO (162 mg, 1.44 mmol) and phenyl triflate (320 μL , 2.00 mmol) afforded **210** (310 mg, 86 %) as a white crystalline solid. Data as above.

(*E*)-Stilbene **210**



210



217

Using General Procedure **18**, $\text{HAlCl}_2 \cdot 2\text{THF}$ (1.03 g, 4.22 mmol), Cp_2TiCl_2 (34.5 mg, 139 μmol), phenylacetylene (310 μL , 2.80 mmol), XPhos (38.9 mg, 81.6 μmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (30.9 mg, 29.9 μmol), DABCO (165 mg, 1.47 mmol) and phenyl triflate (320 μL , 2.00 mmol) afforded **210** (94.6 mg, 26 %) as a white crystalline solid and 1,1-diphenylethylene **217** (163 mg, 45 %) as a colourless oil. Data for **210** as above. Data for **217**: R_F (pentane) 0.38; ^1H NMR (400 MHz, CDCl_3) δ : 7.41-7.31 (br m, 10 H, Ar), 5.49 (s, 2H, CH_2); ^{13}C NMR (100.6 MHz, CDCl_3) δ : 150.1 (Ar_2C), 141.5 (Ar), 128.3 (Ar), 128.1 (Ar), 127.7 (Ar), 114.3 (CH_2). Data were consistent with literature values.¹⁹⁰

5.5.4 Molecular Modelling of Organoaluminium Species

The molecule was constructed in Spartan '06 and minimised with the MMFF94 forcefield. A Hartree-Fock calculation was performed using a 3-21G basis set with optimised geometry and frequencies. The average bond dissociation energy D_{bar} (Al-N) for DABCO-coordinated aluminium species was calculated using Equations 1 and 2, taking the calculated U and H values were taken from the verbose output window. Microsoft Excel 2000 was used for the calculation of values in Equations 1 and 2, with E_{tot} being used to signify the sum of U and H (in kcal mol^{-1}). These values were calculated for the DABCO adduct (EY_n), the uncoordinated aluminium species (E) and the corresponding monocoordinated DABCO species (Y). Data are shown in **Table 26**.

EY_n	n	U(EY_n) (Hartree)	H(EY_n) (kcalmol⁻¹)	E_{tot}(EY_n) (kcalmol⁻¹)	U(E) (Hartree)	H(E) (kcalmol⁻¹)	E_{tot}(E) (kcalmol⁻¹)
DABAL-Me ₂ CCPh	1	-1588.46291	381.8516969	-996395	-623.595	123.6246	-391188.2542
DABAL-Cl ₂ CHCHPh	1	-3263.15914	319.5560707	-2047345	-1460.93	93.47744	-916653.0691
DABAL-Cl ₃	1	-3567.5102	146.6218212	-2238502	-1613.09	7.060325	-1012224.094
DABAL-Me ₃	1	-1058.97726	285.0021989	-664234	-358.86	75.1717	-225112.8586

EY_n	U(Y) (Hartree)	H(Y) (kcalmol⁻¹)	E_{tot}(Y) (kcalmol⁻¹)	nE_{tot}(Y) (kcalmol⁻¹)	Enthalpy of Atomisation (kcalmol⁻¹)	BDE (kcalmol⁻¹)
DABAL-Me ₂ CCPh	-964.81	254.9547	-605173	-605173	-33.369217	-33.3692
DABAL-Cl ₂ CHCHPh	-1802.16	223.8486	-1130650	-1130650	-42.385918	-42.3859
DABAL-Cl ₃	-1954.34	137.6455	-1226229	-1226229	-48.360136	-48.3601
DABAL-Me ₃	-700.067	206.4844	-439093	-439093	-28.409228	-28.4092

Table 26

References

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